COLLECTED PAPERS

from

THE RESEARCH LABORATORY
PARKE, DAVIS & CO.
DETROIT, MICH.

DR. E. M. HOUGHTON, Director.

Reprints—Volume 4
1916

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ON THE PRESENCE OF HISTIDINE-LIKE SUBSTANCES IN THE PITUITARY GLAND (POSTERIOR LOBE).

BY T. B. ALDRICH.

(From the Research Laboratory of Parke, Davis & Co.)

In 1896, A. Kossel discovered among the cleavage products of sturine a basic compound[1] to which he gave the name histidine. Later this compound was found among the cleavage products of complex proteins when these were subjected to acid hydrolysis[2] or to tryptic digestion.[3]

According to Pauly,[4] a solution of histidine made alkaline with sodium carbonate gives a very beautiful diazo-reaction with diazobenzene sulfonic acid, which is deep cherry-red in dilutions of 1:20,000 and still markedly red in 1:100,000. Furthermore it is stated that, with the exception of tyrosine, no other cleavage product from protein, among a large number tested, gives such a color reaction, and that not only can histidine be detected by means of this reaction when mixed with other cleavage products, but also when in the original protein before cleavage, where it is united with other groups, providing the tyrosine is removed or changed so as not to react with this reagent.

As far as investigated by Pauly no other proteid cleavage product outside of histidine and tyrosine gives this reaction. Nearly all give a lemon yellow color in soda solution; such color being given, according to Pauly, by glycocol, alanine, leucine, valine, serine, lysine, ornithine, arginine, asparagine, glutamic acid, cystine, and hippuric acid, while with pyrolidine carboxylic acid and tryptophane no reaction is given. Glucosamine, phenylalanine and oxypyrolidine carboxylic acid, as well as the cleavage products obtained by Skraup[5] from caseine were not available to Pauly, but he states that it is not to be supposed that an exception would be found among these products.[6]

[1] *Z. physiol. Chem.*, 22, 182 (1896).
[2] Hedin, *Ibid.*, 22, 191 (1896).
[3] Kutscher, *Ibid.*, 25, 195 (1898).
[4] *Ibid.*, 42, 513 (1904).
[5] *Ber.*, 37, 3 (1896).
[6] My experience with Pauly's histidine test has shown me that other bodies besides tyrosine and histidine respond to this test, giving a reddish color that might be confusing. Among the bodies tested may be mentioned *p*-oxyphenylethylamine and *B*-iminazolyl-ethylamine.

In the diazo-reaction we have, therefore, a positive means of determining whether protein or protein cleavage products contain histidine or tyrosine, especially as these bodies give a positive reaction where Millon's test is practically negative. The greatest importance seems, however, to lie in the fact that this reaction shows the presence of histidine and tyrosine in protein-like combination. Whenever a protein substance gives Pauly's reaction, then either tyrosine or histidine has been demonstrated among the hydrolytical cleavage products of this protein; while in other proteins where the diazo-reaction was negative these bodies were absent.

Pauly's method[7] of preparing diazobenzene sulfonic acid (which should be prepared fresh every time) and his directions for applying the test are as follows:

1. Preparation of Diazobenzenesulfonic Acid.—Two grams of finely powdered sulfanilic acid are mixed with 3 cc. of water and 2 cc. concentrated hydrochloric acid, forming a thick paste. To this is added in small portions, in less than a minute, cooling after each addition, a gram of potassium nitrite dissolved in 1-2 cc. of water. The sulfanilic acid, for the most part, passes rapidly in solution and there is formed a thick, white crystalline precipitate of diazobenzene sulfonic acid which, after a few minutes, is filtered off by suction and washed with a little cold water. Any unchanged sulfanilic acid does not influence the reaction.

2. Reaction with Histidine.—To the solution to be tested, having demonstrated the absence of tyrosine by Millon's reagent, an excess of sodium carbonate (preferred to caustic soda) is added, and then 3-5 cc. of an alkaline carbonate solution of a few centigrams of the diazobenzene sulfonic acid prepared at the time of testing. Within three minutes at the longest, usually immediately, a dark cherry-red color appears, which even by dilution with many times its volume of water, retains is red color and does not shade into yellow. By acidulating, the color passes into a pure orange color.

Quite recently, K. Inouye,[8] working in Kossel's laboratory, published a method for detecting histidine in the presence of tyrosine, employing the above reaction. According to this investigator, the reaction is also given even when histidine is in com-

[7] Pauley, *Loc. cit.*

[8] Z. [illegible] 83, 79 (1912).

bination with the protein molecule, and were it not for the fact that tyrosine, free or attached to protein, gives a very similar red color reaction with diazobenzene sulfonic acid, it would be a comparatively simple matter to detect histidine, just as tyrosine and tryptophane are recognized by color tests.

Since tyrosine gives with diazobenzene sulfonic acid, in alkaline solution, a color reaction that can not be distinguished from that of histidine, Inouye modified the test so as to eliminate the tyrosine from the reaction. This modification was brought about by benzoylating in alkaline soda solution.

If one shakes a solution of tyrosine with a few drops of benzoylchloride until the odor of the chloride has disappeared, after making alkaline with soda solution, the addition of diazobenzene sulfonic acid to the filtrate does not produce the characteristic color. If, on the other hand, one benzoylates histidine by the same process, the color reaction persists.

It was expected, according to Inouye, that this reaction for recognizing histidine would be applicable when histidine was united with protein or other complexes; but this expectation was not realized; for, after benzoylating such bodies, the color reaction could not be obtained, and it was found necessary to hydrolyze these substances either with the help of acids or by digestion with trypsin in order to establish the presence of histidine.

Having observed several years ago that pituitary preparations, obtained from the posterior lobe, gave a marked histidine reaction, I was led to infer either the presence of histidine or some such body, but at that time, no method had been worked out to recognize histidine in the presence of tyrosine. On the appearance of Inouye's communication referred to above, I concluded to use his method for determining the presence of histidine in this lobe, the result of which investigations are given below:

EXPERIMENTAL.

The material employed was the desiccated defatted posterior lobe of the pituitary gland (consisting for the greater part of protein) prepared in the usual way, and a purified product soluble in water. (Three tests were made in all.)

Hydrolysis by Acid.—(1) 0.5 g. of desiccated product was boiled for 5 hours (employing a return condenser) with 100 cc. of water, to which

was added 2.5 cc. of concentrated hydrochloric acid. It was then evaporated on the steam bath to a syrupy consistency, taken up in water, an excess of lead oxide added, and the mixture warmed on the steam bath. After cooling it was made alkaline with sodium carbonate solution, filtered, and brought up to 80 cc.

(*a*) 10 cc. of the above were taken (representing 63 mg. of the original powder), 0.5 cc. saturated sodium carbonate solution and then 3 drops of benzoyl chloride were added and the mixture was agitated until the odor of the chloride had disappeared. It was then filtered and Pauly's test applied as follows:

5 cc. (32 mg.) + 4 drops of sodium carbonate saturated solution + 30 mg. of diazobenzene sulfonic acid either in solid form or dissolved in water. *Color reaction very pronounced.*

(*b*) 10 cc. + 1½ cc. saturated sodium carbonate solution + 15 drops of benzoyl chloride, etc. *Reaction pronounced but not as strong as by(a).*

(2) 0.5 g. of the perfectly soluble product, treated as by (1). Made up to 80 cc.

(*a*) 10 cc. taken + 1½ cc. of saturated sodium carbonate solution + 15 drops of benzoyl chloride, etc., etc.

Pauly's reaction pronounced, but less so than the original product.

Without Hydrolysis.—(3) 0.5 g. (perfectly soluble product) dissolved in 25 cc. H_2O, 3 cc. of saturated sodium carbonate solution added then 20 drops of benzoyl chloride. The resulting solution worked up in the usual way, *gave a strong Pauly's reaction.*

(4) Repeated (3) *Pauly's reaction pronounced.*

Hydrolysis by Trypsin.—(1) 0.2 g. pancreatin was agitated with 40 cc. of a 0.5% sodium carbonate solution.

(*a*) To 20 cc. of the above was added 0.5 g. of desiccated posterior lobe powder, and a few drops of chloroform. Placed in incubator for about 2 days.

(*b*) The remaining 20 cc. of (5) was also placed in incubator, a little chloroform being added.

Both (*a*) and (*b*) were agitated from time to time.

At the end of 2 days both solutions were evaporated (after neutralizing with hydrochloric acid) to a small volume, made alkaline, then benzoylated and eventually filtered. Both gave Pauly's reaction, but the color given by (*a*) was more intense.

It might be stated at this point that both powders gave Millon's test before as well as after hydrolysis; but that after benzoylating, this reaction was always negative.

In the above experiments I have purposely used a large excess of benzoyl chloride and sufficient sodium carbonate solution to maintain an alkaline reaction. Inouye states that he used only a few drops; but in every case after thorough benzoylating I found

even with a large excess of benzoyl chloride that the solution gave a positive reaction. In some instances the color was not as pronounced as one would expect, but this might be accounted for by the larger amount of benzoyl chloride used, or the fact that all was not decomposed, or that the presence of benzoic acid or its salts influenced the same.

One would conclude from the above, if Inouye's observations are correct, that histidine is present in the above preparations, prepared from the pituitary gland, were it not for the fact that the solutions before or after hydrolysis or after benzoylating failed to give in my hands Weidel's reaction as modified by Fisher or Knoop's bromine reaction. Whether we are justified, however, in drawing this conclusion is questionable, for it may be assumed that other bodies are present which interfere with the reaction or that histidine is present in two small an amount.

Under hydrolysis by trypsin the presence of a small amount of histidine in the *control* is explained by its presence in the pancreatin employed.

From (3) without hydrolysis, it would seem that at least one of the histidine-like substances in the pituitary gland (posterior) is not united to protein, for after benzoylating, employing an excess of sodium carbonate, the filtrate gave a strong Pauly's reaction. It is quite probable that we have a free and possibly a combined histidine or histidine-like compound. We are also confronted by the possibility of several substances of this nature being present. This latter view having support from the work of Fühner[1] who claims to have isolated four distinct substances from the posterior lobe of the pituitary gland, all of which give Pauly's reaction.

What compound or compounds we have to deal with here is suppositional at present, although evidence seems to be accumulating that points not to histidine but to some histidine-like compounds similar to histamine.[2] This view is also shared by Fühner,[3] who says: "According to the work of others and myself I am led to conclude that histamine and the active principle of the posterior lobe of the gland are probably not identical; but pharmacologically directly related."

[1] *Deutsche Med. Wochschr.*, 39, 491 (1913).
[2] Histamine is the commercial name for *B*-Iminazolylethylamine.
[3] *Munch. Med. Wochschr.*, 599, 852 (1913).

CONCLUSIONS.

1. It would seem that histidine (or some such compound or compounds) is contained in the desiccated posterior lobe of the pituitary gland.

2. These substances are probably in a more or less free state, or in some combination other than protein.

3. The compounds giving Pauly's reaction are probably not histidine, since Weidel's reaction, as modified by Fischer, or Knoop's reaction with bromine were both negative.

4. Pauly's reaction is not a specific reaction for histidine, unless other compounds, such tyrosine, *p*-oxyphenylethylamine, *B*-iminazolylethylamine, adrenalin, etc., are removed; but a general reaction for a class of compounds yet to be determined.

REPRINTS OF PUBLICATIONS FROM THE RESEARCH LABORATORY, PARKE, DAVIS & CO., DETROIT, MICH.

The present system of collecting reprints of articles published from the Research Laboratory was begun in 1912. Reprints of the following articles published subsequent to that time are available and will be sent upon request. The publications marked (*) are no longer available.

1. On the Administration of Diphtheria Toxin in a Collodion Sac. By E. C. L. Miller. (*Journal of Infectious Diseases,* Vol. 8, January, 1911, pp. 50-65.)

2. A Further Contribution to Our Knowledge of Insecticides—Fumigants. By Chas. T. McClintock, H. C. Hamilton and F. B. Lowe. (*Journal of the American Public Health Association,* Vol. 1, April, 1911, pp. 227-238.)

3. Duboisia Hopwoodii—A Histological Study. By Oliver A. Farwell. (Reprinted from *Merck's Report,* Vol. 20, May 1, 1911.)

*4. Etiology of Canine Distemper. By Newell S. Ferry. (*Journal of Infectious Diseases,* Vol. 8, June, 1911, pp. 399-420.)

*5. The Resistance of Smallpox Vaccine to the Coal-tar Disinfectants. By Chas. T. McClintock and Newell S. Ferry. (*Journal of the American Public Health Association,* Vol. 1, June, 1911, pp. 418-419.)

6. Production of Immunity with Over-Neutralized Diphtheria Toxin. By Chas. T. McClintock and Newell S. Ferry. (*Abdruck Aus Dem Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten,* Abt. 1, Originale, Bd. 59, July 15, 1911, pp. 456-464.)

7. Soaps from Different Glycerides—Their Germicidal and Insecticidal Values Alone and Associated with Active Agents. By H. C. Hamilton. (*Journal of Industrial and Engineering Chemistry,* Vol. 3, August, 1911, pp. 582-584.)

*8. The Sleepy Grass of New Mexico: A Histological Study. By Oliver A. Farwell. (*Merck's Report,* Vol. 20, October, 1911, pp. 271-273.)

*9. Some Observations on the Physiological Action of Sleepy Grass. By A. W. Lescohier. (*Merck's Report,* Vol. 20, October, 1911, pp. 271-275.)

*10. An Investigation of the Depressor Action of Pituitary Extracts. By Carey P. McCord. (*Archives of Internal Medicine,* Vol. 8, November, 1911, pp. 609-620.)

11. The Physiology of the Pituitary Gland and the Actions of Its Extracts. By Carl J. Wiggers. (*American Journal of Medical Sciences,* Vol. 141, April, 1911, pp. 502-515.)

12. A Physiological Investigation of the Treatment of Hemoptysis. By Carl J. Wiggers. (*Archives of Internal Medicine,* Vol. 8, 1911, pp. 17-38.)

13. Notes on Catgut Sterilization: A Preliminary Report. By Willard H. Hutchings. (*Annals of Surgery,* Vol. 54, July, 1911, pp. 693-695.)

14. The Relations of Pyogenic Microorganisms to the Etiology and Treatment of Skin Diseases. By Henry Rockwell Varney. (*Ohio State Medical Journal,* December, 1911.)

15. A Micrococcus with Unusual Characteristics as a Factor in a Resistant Dermatosis Resembling Acne Vulgaris. By Henry Rockwell Varney and L. T. Clark. (*Journal of Cutaneous Diseases,* Vol. 30, February, 1912, pp. 72-78.)

16. Serum Treatment of Hemorrhage and Blood Dyscrasias. By A. W. Lescohier. (*New York Medical Journal,* Vol. 95, February 3, 1912, pp. 223-229.)

*17. Further Studies on the Bacillus Bronchicanis, the Cause of Canine Distemper. By Newell S. Ferry. (*American Veterinary Review,* Vol. 41, April, 1912, pp. 77-79.)

18. The Pharmacopœial Requirements for Cannabis Sativa. By H. C. Hamilton. (*Journal of the American Pharmaceutical Association,* Vol. 1, March, 1912, pp. 200-203.)

19. The Heart Tonic Unit. By H. C. Hamilton. (*American Journal of Pharmacy,* Vol. 84, March, 1912, pp. 97-103.)

20. Studies on the Etiology of Equine Influenza. By Newell S. Ferry. (*Veterinary Journal* (London), Vol. 19, April, 1912, pp. 185-197.)

21. A Method for the Bacteriological Standardization of Disinfectants. By Tatsuzo Ohno and H. C. Hamilton. (*American Journal of Public Health,* Vol. 2, May, 1912, pp. 331-338.)

22. Physiological Testing. By E. M. Houghton. (*American Druggist,* July and September, 1911, and January and April, 1912.)

23. Bacillus Bronchisepticus (Bronchicanis): The Cause of Distemper in Dogs and a Similar Disease in Other Animals. By Newell S. Ferry. (*Veterinary Journal* (London), Vol. 19, July, 1912, pp. 376-391.)

24. On Feeding Young Pups the Anterior Lobe of the Pituitary Gland. By T. B. Aldrich. (*American Journal of Physiology,* Vol. 30, July, 1912, pp. 352-357.)

25. A Practical Portable Incubator. By Newell S. Ferry. (*Abdruck Aus Dem Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten,* Abt. 1, Original, Bd. 65, Heft 4/5, 1912, pp. 412-413.)

26. Tobacco Extracts: Their Comparative Values as Insecticides. By W. O. Hollister. (*Journal of Economic Entomology,* Vol 5, June, 1912, pp. 263-267.)

27. The Pharmacological Assay of Pituitary Preparations. By H. C. Hamilton. (*Journal of the American Pharmaceutical Association,* Vol. 1, October, 1912, pp. 1117-1119.)

28. Pituitary Extracts in Obstetrics and Gynecology. By A. W. Lescohier and O. E. Closson. (*Journal of the Michigan State Medical Society,* Vol. 11, October, 1912, pp. 650-657.)

29. Biological Products—Veterinary. By Robert H. Wilson. (*American Veterinary Review,* Vol. 41, September, 1912, pp. 668-681.)

30. The Isolation and Cultural Characteristics of Bacillus Acne. By Edwin M. Stanton. (*Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten,* Original, Bd. 66, Heft 5/7, 1912, pp. 386-389.)

31. Studies on Hog Cholera. By Walter E. King and Robert H. Wilson. (*Journal of Infectious Diseases,* Vol. 11, Nov., 1912, pp. 441-458.)

32. Studies on the Virus of Hog Cholera. By Walter E. King and F. W. Baeslack. (*Journal of Infectious Diseases,* Vol. 12, Jan., 1913, pp. 39-41.)

33. The Physiological Activity of Cannabis Sativa. By H. C. Hamilton, A. W. Lescohier and R. A. Perkins. (*Journal of the American Pharmaceutical Association,* Vol. 2, Jan., 1913, pp. 22-30.

34. The Iodine Content of the Small, Medium and Large Thyroid Glands of Sheep, Beef and Hogs. By T. B. Aldrich. (Original Communications, Eighth International Congress of Applied Chemistry, Vol. 19, 1912, pp. 9-14.)

35. Studies on the Virus of Hog Cholera. By Walter E. King and Robert H. Wilson. (*Zeitschrift für Immunitatsforschung und Experimentelle Therapie,* Bd. 16, Heft 3, 1913, pp. 367-376.)

36. On the Cultivation of the Treponema Pallidum (Spirochæta Pallida). By F. W. Baeslack. (*Journal of Infectious Diseases,* Vol. 12, Jan., 1913, pp. 55-67.)

*37. Studies on the Gonococcus, I. By Carl C. Warden. (*Journal of Infectious Diseases,* Vol. 12, Jan., 1913, pp. 93-105.)

38. Studies on the Virus of Hog Cholera. By Walter E. King, F. W. Baeslack and George L. Hoffmann. (*Journal of Infectious Diseases,* Vol. 12, March, 1913, pp. 206-235.)

39. Bacillus Bronchisepticus—Its Relation to Canine Distemper. By N. S. Ferry. (*American Veterinary Review,* Vol. 43, April, 1913, pp. 16-30.)

40. Drug Influence on Extrasystoles of the Mammalian Heart. By Carey P. McCord. (*Interstate Medical Journal,* Vol. 19, Oct., 1912, pp. 870-880.)

41. The Employment of Protective Enzymes of the Blood as a Means of Extracorporeal Diagnosis. I.—Sero-Diagnosis of Pregnancy. By Carey P. McCord. (*Surgery, Gynecology and Obstetrics,* Vol. 16, April, 1913, pp. 418-421.)

42. Tribromo-tert-Butyl Alcohol, $C_4H_7OBr_3$. By T. B. Aldrich. (*Journal of the American Chemical Society,* Vol. 33, March, 1911, pp. 386-388.)

43. On Feeding Young White Rats the Posterior and the Anterior Parts of the Pituitary Gland. By T. B. Aldrich. (*American Journal of Physiology,* Vol. 31, Nov., 1912, pp. 94-101.)

44. The Rationale of the Use of Adrenalin in the Treatment of Asthma. By Carey P. McCord. (*Medical Record,* Vol. 83, March 8, 1913, pp. 431-432.)

45. Standardization of Disinfectants: Some Suggested Modifications. By H. C. Hamilton and T. Ohno. (*American Journal of Public Health* Vol. 3, June, 1913, pp. 582-588.)

46. Preventive Measures Against Equine Influenza Based on Its Bacteriology. By N. S. Ferry. (Report of the Proceedings of the United States Live Stock Association, December, 1912, p. 127.)

47. Correcting Water. By H. C. Hamilton. (*Bulletin of Pharmacy,* Vol. 27, August, 1913, pp. 330-335.)

48. Duration of Immunity Following Small-pox Vaccination. By A. W. Lescohier. (*Journal of the American Medical Association,* Vol. 61, Aug. 16, 1913, page 487-490.)

49. On Crystalline Kombe-Strophanthin. By D. H. Brauns and O. E. Closson. (*Journal of the American Pharmaceutical Association,* May, June and July, 1913, Vol. 2.)

50. A Comparative Study of Antigens for the Wassermann Reaction. By H. R. Varney and F. W. Baeslack. (*Journal of the American Medical Association,* Vol. 61, Sept. 6, 1913, pp. 754-757.)

51. The Treatment of Tetanus. By Charles T. McClintock and Willard H. Hutchings. (*Journal of Infectious Diseases,* Vol. 13, Sept., 1913, pp. 309-320.)

52. Spirochæta Suis, Its Significance as a Pathogenic Organism, Studies on Hog Chlorea. By Walter E. King and George L. Hoffmann. (*Journal of Infectious Diseases,* Vol. 13, Nov., 1913, pp. 463-498.)

53. Time Recorder for Kymograph Tracings. By Oliver E. Closson. (*Journal of Pharmacology and Experimental Medicine,* Vol. 5, Jan., 1914, pp. 235-238.)

54. U. S. P. Menstrua. By H. C. Hamilton. (*American Journal of Pharmacy,* Vol. 86, Feb., 1914, pp. 56-61.)

55. Numerical Variations of the White Blood Cells in Mice Inoculated with Transplantable Adenocarcinoma. By F. W. Baeslack. (*Zeitschrift für Immunitatsforschung und Experimentelle Therapie,* Bd. 20, Heft 5, 1914, pp. 421-435.)

56. A Study of the Germicidal Action of the Ultraviolet Rays. By E. M. Houghton and L. Davis. (*American Journal of Public Health,* Vol. 4, March, 1914, pp. 224-240.)

57. Some Phenomena Involved in the Life History of Spirochæta Suis—Studies on Hog Cholera. By W. E. King and R. H. Drake. (*The Journal of Infectious Diseases,* Vol. 14, March, 1914, pp. 246-250.)

58. The Sterilization of Adrenalin Solutions. By L. W. Rowe. (*American Journal of Pharmacy,* Vol. 86, April, 1914, pp. 145-149.)

59. Infection and Immunity: A Review. By N. S. Ferry, Ph.B., M.D. (*Journal of the American Pharmaceutical Association,* Vol. 3, April and May, 1914.)

60. Disinfection—What Disinfectant is the Most Generally Applicable for Clinical, Surgical and Sanitary Purposes? By H. C. Hamilton. (*Therapeutic Gazette,* Vol. 38, May, 1914, pp. 311-315.)

61. Study of the Bacteriology of the Posterior Nasopharynx in Scarlatina. By N. S. Ferry, M.D. (*Medical Record,* Vol. 85, May 23, 1914, pp. 934-935.)

62. Some Experiences with Bacterial Vaccines in Scarlatina. By Guy L. Kiefer, M.D., D.P.H., and N. S. Ferry, M.D. (*Medical Record,* Vol. 85, May 23, 1914, p. 936.)

63. A Sero-enzyme Test for Syphilis. By F. W. Baeslack, M.A., M.D. (*The Urologic and Cutaneous Review,* Vol. 18, May, 1914, pp. 234-238.)

64. Bacteriology and Control of Acute Infections in Laboratory Animals. By N. S. Ferry, Ph.B., M.D. (*Journal of Pathology and Bacteriology,* Vol. 18, 1914, pp. 445-455.)

65. The Bacteriological Standardization of Disinfectants. By H. C. Hamilton and Tatsuzo Ohno. (*American Journal of Public Health,* Vol. 4, No. 6, p. 163.)

66. The Pineal Gland in Relation to Somatic, Sexual and Mental Development. By Carey P. McCord, M.D. (*Journal of the American Medical Association,* Vol. 63, July 18, 1914, pp. 232-235.)

67. The Sero-enzyme Test for Syphilis. By F. W. Baeslack, M.D., M.A. (*Journal of the American Medical Association,* Vol. 63, Aug. 15, 1914, pp. 559-563.)

68. A Case of Contagious Broncho-pneumonia Caused by Bacillus Coli Communis. By Edwin M. Stanton. (*American Veterinary Review,* Vol. 14, May, 1914, pp. 233-235.)

69. Local Anesthetics—Some Comparative Physiological Reactions. By Oliver E. Closson. (*Journal of the Michigan State Medical Society,* Vol. 13, Oct., 1914, pp. 587-597.)

70. Potassium Tellurite as an Indicator of Microbial Life. By Walter E. King and Lewis Davis. (*American Journal of Public Health,* Vol. 4, Oct., 1914, pp. 917-932.)

71. Further Studies with Reference to Spirochetes Observed in Swine —Studies on Hog Cholera. By Walter E. King, Raymond H. Drake, and Geo. L. Hoffmann. (*Zeitschrift für Immunitätsforschung und Experimentelle Therapie,* Vol. 22, 1914, pp. 347-371.)

72. The Pharmacy of Adrenalin. By C. P. Beckwith. (*Journal of the American Pharmaceutical Association,* Vol. 3, November, 1914, pp. 1547-1554.)

73. A Study of the "Tellurite Reaction" with the Colon-typhoid Group and other Organisms. By Lewis Davis, S.M. (*Centralblatt für Bakteriologie Parasitenkunde und Infektionskrankheiten,* 75 Band, 1914, pp. 180-192.)

74. An Expanding Root Canal Filling. By George Bailey Harris, D.D.S., Sc.M. (*Items of Interest,* Vol. 36, Dec., 1914, pp. 881-886.)

75. On the Presence of Histidine-like Substances in the Pituitary Gland (Posterior Lobe). By T. B. Aldrich. (*Journal of the Chemical Society,* Vol. 37, Jan., 1915, pp. 203-208.)

INOCULATION EXPERIMENT WITH PURE CULTURE OF SPIROCHAETA HYOS.

STUDIES ON HOG-CHOLERA.

WALTER E. KING AND RAYMOND H. DRAKE.

(From the Research Laboratory of Parke, Davis & Company, Detroit, Michigan.)

In former publications it has been suggested that the spirochæta hyos may bear some etiological relationship to hog-cholera. Heretofore, it has not been possible to prove the pathogenic significance of this new organism because of the difficulties encountered in attempting to obtain pure cultures. These difficulties have not been completely overcome as yet, but, by painstaking effort, a pure culture of the spirochæta hyos has been secured and typical hog-cholera of the acute type has been produced with this culture. The protocol of this experiment is as follows:

On September 23, 1913, a culture was made on Hata medium with rabbit kidney from Berkefeld filtered suspension of tissue from a local lesion on the ear of Hog 653. The local ear lesion, on dark-field examination, showed numerous spirochetes. Hog 653, on autopsy, showed typical lesions of hog-cholera.

Culture 653, from the ear, was incubated in a desiccator, under anaerobic conditions, for several weeks at 40° C., and then for several weeks at 37° C. Dark-field examination, on December 13, showed the presence of spirochetes, relatively few in number. A portion of the impure culture was macerated in sterile water and filtered twice through the Berkefeld.

On January 5, 1914, cultures were made from the filtrate on Hata medium with no kidney tissue. Control cultures from the filtrate gave negative tests, showing that the filtrate was free from bacteria.

Culture 653, grown in the same manner as the above, was examined on March 17, on dark-field. It showed growth of the spirochæta hyos in pure culture. Culture media, inoculated with material from Culture 653 (Transfer 1), gave negative results.

A suspension was made of a portion of pure culture of the spirochæta hyos (Culture 653, Transfer 1) in an equal volume of sterile water. Dark-field examination showed the spirochæta hyos, uncontaminated, in suspension. On March 17, animal inoculations were made from the suspension as follows: Hog 805, 4.5 c.c; Hog 806, 3.5 c.c.—both intramuscularly. A normal hog, Hog 807, was placed with them in an isolated, disinfected room as a control on Hogs 805 and 806.

Hog 805.—On March 17, Hog 805 was injected intramuscularly with 4.5 c.c. of Culture 653 (Transfer 1); March 25, the hog appeared normal,

appetite good, but somewhat inactive; March 27, normal in every way; April 6, "off feed," appeared sick; April 8, was bright; April 15, very sick; April 20, died.

Inguinal, mesenteric, retroperitoneal and other lymphatic glands were enlarged and very hemorrhagic; lungs, congested and consolidated; liver, mottled with areas of degeneration; spleen, much enlarged, dark and soft; kidneys, ecchymotic; intestinal mucosa, congested; no typical ulcers. Spirochæta hyos present in cecal mucosa.

Hog 806.—On March 17, Hog 806 was injected intramuscularly with 3.5 c.c. of Culture 653 (Transfer 1); March 26, the hog was inactive, anorexia; March 27, acted better, appetite better; March 30, anorexia, weak, constipated; April 2, no appetite, back arched; April 6, numerous spirochetes in exudate from ear; April 8, very sick; April 13, moribund, killed.

Figure 1.—Hog 806.

Lymphatic glands were very enlarged and hemorrhagic; liver, normal; lungs, congested and consolidated; spleen, soft and friable, enlarged; kidney, ecchymotic; small button ulcers in mucosa of large intestine. Spirochæta hyos in mucosa of cecum.

Hog 807.—Hog 807 was a control on culture pigs. On March 17 the hog was placed with Hogs 805 and 806; April 1, normal, good appetite; April 2, slight symptoms; April 6, sick; April 7, anorexia; April 8, sick, constipated; April 15, very sick; April 17, died.

Lymphatic glands much enlarged and hemorrhagic; lungs, congested and consolidated; spleen, soft and friable, enlarged; kidneys, ecchymotic; small ulcers in mucosa of cecum, mucosa of large intestine congested. Spirochæta hyos present in margins of cecal ulcers.

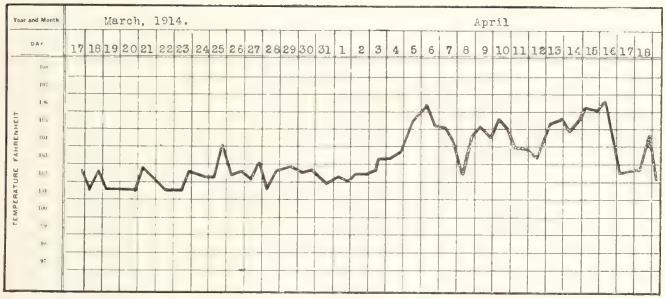

Chart 1.- Temperature Curve for Hog 805.

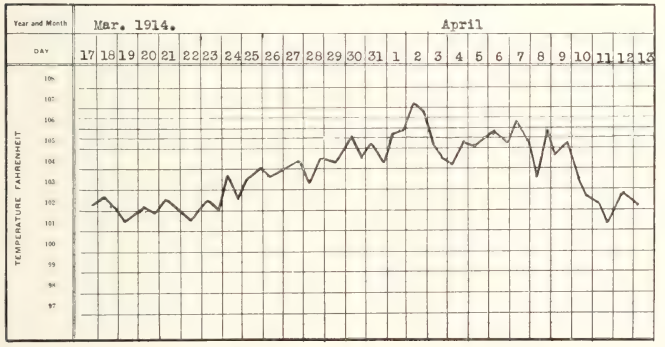

Chart 2. Temperature Curve for Hog 806.

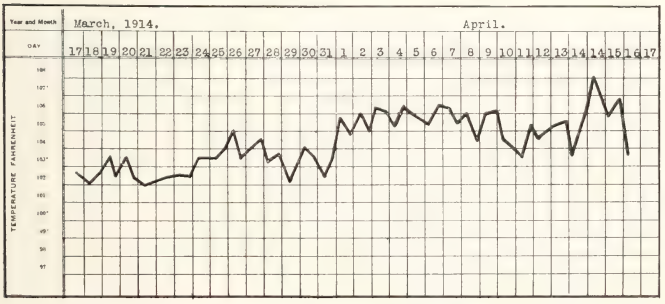

Chart 3. Temperature Curve for Hog 807.

In this experiment Hog 805 showed a mild reaction eight days after inoculation and manifested "secondary" symptoms twenty days after inoculation. This interesting phenomenon, which has been observed in some ten or twelve cases of hog-cholera produced by inoculating impure cultures of the spirochæta hyos into healthy hogs, may represent the period of time necessary for certain stages of development of the spirochete to occur in the animal body.

Hog 806 acquired typical hog-cholera of the acute type from the inoculation with pure culture of the spirochæta hyos, as controlled by the failure of symptoms to appear in the case of Check-Hog 807 until a sufficient time had elapsed for the control animal to acquire the disease by contagion.

The inoculation experiment should be repeated with other strains in pure culture before final conclusions are drawn. However, until substantial negative data can be presented by other investigators, the successful production of the disease with a pure culture of the spirochæta hyos, together with other data already presented, justifies the statement: "Spirochæta hyos is more nearly established as the specific cause of hog-cholera than any other known organism."

REPRINTS OF PUBLICATIONS FROM THE RESEARCH LABORATORY, PARKE, DAVIS & CO., DETROIT, MICH.

The present system of collecting reprints of articles published from the Research Laboratory was begun in 1912. Reprints of the following articles published subsequent to that time are available and will be sent upon request. The publications marked (*) are no longer available.

1. On the Administration of Diphtheria Toxin in a Collodion Sac. By E. C. L. Miller. (*Journal of Infectious Diseases,* Vol. 8, January, 1911, pp. 50-65.)

2. A Further Contribution to Our Knowledge of Insecticides—Fumigants. By Chas. T. McClintock, H. C. Hamilton and F. B. Lowe. (*Journal of the American Public Health Association,* Vol. 1, April, 1911, pp. 227-238.)

3. Duboisia Hopwoodii—A Histological Study. By Oliver A. Farwell. (Reprinted from *Merck's Report,* Vol. 20, May 1, 1911.)

*4. Etiology of Canine Distemper. By Newell S. Ferry. (*Journal of Infectious Diseases,* Vol. 8, June, 1911, pp. 399-420.)

*5. The Resistance of Smallpox Vaccine to the Coal-tar Disinfectants. By Chas. T. McClintock and Newell S. Ferry. (*Journal of the American Public Health Association,* Vol. 1, June, 1911, pp. 418-419.)

6. Production of Immunity with Over-Neutralized Diphtheria Toxin. By Chas. T. McClintock and Newell S. Ferry. (*Abdruck Aus Dem Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten,* Abt. 1, Originale, Bd. 59, July 15, 1911, pp. 456-464.)

7. Soaps from Different Glycerides—Their Germicidal and Insecticidal Values Alone and Associated with Active Agents. By H. C. Hamilton. (*Journal of Industrial and Engineering Chemistry,* Vol. 3, August, 1911, pp. 582-584.)

*8. The Sleepy Grass of New Mexico: A Histological Study. By Oliver A. Farwell. (*Merck's Report,* Vol. 20, October, 1911, pp. 271-273.)

*9. Some Observations on the Physiological Action of Sleepy Grass. By A. W. Lescohier. (*Merck's Report,* Vol. 20, October, 1911, pp. 271-275.)

*10. An Investigation of the Depressor Action of Pituitary Extracts. By Carey P. McCord. (*Archives of Internal Medicine,* Vol. 8, November, 1911, pp. 609-620.)

11. The Physiology of the Pituitary Gland and the Actions of Its Extracts. By Carl J. Wiggers. (*American Journal of Medical Sciences,* Vol. 141, April, 1911, pp. 502-515.)

12. A Physiological Investigation of the Treatment of Hemoptysis. By Carl J. Wiggers. (*Archives of Internal Medicine,* Vol. 8, 1911, pp. 17-38.)

13. Notes on Catgut Sterilization: A Preliminary Report. By Willard H. Hutchings. (*Annals of Surgery,* Vol. 54, July, 1911, pp. 693-695.)

14. The Relations of Pyogenic Microorganisms to the Etiology and Treatment of Skin Diseases. By Henry Rockwell Varney. (*Ohio State Medical Journal,* December, 1911.)

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16. Serum Treatment of Hemorrhage and Blood Dyscrasias. By A. W. Lescohier. (*New York Medical Journal,* Vol. 95, February 3, 1912, pp. 223-229.)

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19. The Heart Tonic Unit. By H. C. Hamilton. (*American Journal of Pharmacy,* Vol. 84, March, 1912, pp. 97-103.)

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21. A Method for the Bacteriological Standardization of Disinfectants. By Tatsuzo Ohno and H. C. Hamilton. (*American Journal of Public Health,* Vol. 2, May, 1912, pp. 331-338.)

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43. On Feeding Young White Rats the Posterior and the Anterior Parts of the Pituitary Gland. By T. B. Aldrich. (*American Journal of Physiology,* Vol. 31, Nov., 1912, pp. 94-101.)

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45. Standardization of Disinfectants: Some Suggested Modifications. By H. C. Hamilton and T. Ohno. (*American Journal of Public Health* Vol. 3, June, 1913, pp. 582-588.)

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62. Some Experiences with Bacterial Vaccines in Scarlatina. By Guy L. Kiefer, M.D., D.P.H., and N. S. Ferry, M.D. (*Medical Record,* Vol. 85, May 23, 1914, p. 936.)

63. A Sero-enzyme Test for Syphilis. By F. W. Baeslack, M.A., M.D. (*The Urologic and Cutaneous Review,* Vol. 18, May, 1914, pp. 234-238.)

64. Bacteriology and Control of Acute Infections in Laboratory Animals. By N. S. Ferry, Ph.B., M.D. (*Journal of Pathology and Bacteriology,* Vol. 18, 1914, pp. 445-455.)

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70. Potassium Tellurite as an Indicator of Microbial Life. By Walter E. King and Lewis Davis. (*American Journal of Public Health,* Vol. 4, Oct., 1914, pp. 917-932.)

71. Further Studies with Reference to Spirochetes Observed in Swine —Studies on Hog Cholera. By Walter E. King, Raymond H. Drake, and Geo. L. Hoffmann. (*Zeitschrift für Immunitätsforschung und Experimentelle Therapie,* Vol. 22, 1914, pp. 347-371.)

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WHAT IS THE BEST END-POINT OF THE REACTION IN THE FROG-HEART METHOD OF DIGITALIS ASSAY?*

BY H. C. HAMILTON AND L. W. ROWE.

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While there are various methods in use for standardizing the digitalis series of heart tonics, the frog-heart method devised and introduced by Houghton,[1] in 1894, has perhaps been most widely used in more or less modified form.

These modifications are specifically due to differences of opinion as to the proper length of time after dosing to note the end-point of the reaction, namely, the characteristic systolic stand-still of the heart or the death of the animal with its heart in systole.

The original method made use of the minimal lethal dose, or smallest dose capable of causing the death with heart in systole, of a majority of the frogs to which a certain amount of the preparation in question had been administered. In a somewhat amplified form[2] the method was presented before this Society in 1909.

In 1902, Famulener and Lyons[3] described a method which has been in use in the University of Michigan Pharmacology Department for some time, according to Edmunds.[4] This consists, in brief, in administering such a dose of a digitalis heart-tonic to a frog as to cause paralysis of the heart in systole in one hour. Edmunds' modification differs only in having complete stoppage of the heart—not only systolic but auricular as well.

Barger and Shaw[5] used the same method of injection, namely, into the dorsal lymph-sac, but the frogs were kept under observation until the heart stopped, which they found was within three hours if at all.

Fraenkel[6] practically limited the time to one hour, although a range from thirty-five to one hundred minutes is allowable in his modification.

Ziegenbein[7] used the modification originated by Hans and

*Read before the Scientific Section, A. Ph. A., at the 62d Annual Convention.

Arthur Meyer of fastening male frogs to a board and exposing the heart before injection. The solution is injected into the thigh lymph-sac and in such a quantity as to produce systolic standstill in two hours.

Gottlieb[8] used as his unit "The smallest amount of the solution which will call forth systolic standstill of the heart of a 30 gm. frog in exactly thirty minutes."

Focke first published his modification of the frog-heart method in 1902.[9] This has been changed somewhat, but is essentially to determine the minimum dose causing systolic standstill in seven to fifteen minutes.

His method is more complicated than the others because of his taking into account the time period. The value of a sample is the result obtained by dividing the frog weight by the product of the dose multiplied by the time. This makes the element of time a very important factor. Delayed absorption or exceptional resistance will lower the apparent value greatly.

While at this time we are not considering suggested methods for standardizing the heart tonics of the digitalis series, other than by the use of frogs, it is not inappropriate to refer to the use of the warm-blooded animals. For example, Hatcher's cat method,[10] Reed and Vanderkleed's guinea-pig method,[11] Heinz's mouse method,[12] and the use of rabbits or dogs to determine the blood pressure and heart action, are all valuable. But for obtaining a fairly accurate estimation of the relative values of two preparations they do not appear to offer any material advantage over the frog-heart method first suggested and used for this purpose. Not only this, but cost, convenience and lack of general adaptability have prevented any extended application of them.

Edmunds and Hale[13] concluded that because in most cases the toxic action is not on the heart but on the respiratory centers, "Methods which employ as a standard the minimum lethal dose obtained from the higher animals are not applicable to the physiological assay of the digitalis series."

The frog-heart method may be considered to have three distinct modifications or that there are two modifications of the original twelve-hour method of Houghton, namely, the so-called short time method of Focke, and the one-hour method of Famulener and Lyons.

The twelve-hour method of Houghton is distinctly one allowing the total toxic effect of the drug to take place. The animal dies or recovers. A more or less total paralysis of the whole heart or of the ventricles may have taken place in many of the test animals, but unless this occurred and resulted in the death of a majority of five or more frogs following the injection of a certain quantity of the drug, a larger quantity must be chosen as the minimal dose. Delayed absorption therefore due to the nature of the drug will not vitiate the results: even digitalis has every opportunity to exert its characteristic effect.

During a large part of the year this takes place in three or four hours, or even less, in the case of Strophanthus, but during the winter months and especially if the water in which they are kept is very cold the final result may be delayed considerably more than twelve hours.

If, however, we limit the time to one hour, or to ten minutes, and expect the drug to show its whole range of action, from therapeutic through to toxic, it is probably demanding the impossible of such a complex mixture as a fluidextract of digitalis. Absorption could not be complete in ten minutes and possibly not in one hour.

If the sample were a pure principle to be tested in comparison with a standard of like properties, the results should be comparable, otherwise the uncertainties of a physiological assay are considerably increased. Edmunds and Hale[13] conclude "that between these two methods (the twelve-hour and one-hour) it is largely a question of personal preference or convenience as far as can be judged in the light of our present knowledge."

Focke's short-time method gives such inaccurate results, is so complicated, and is open to such extreme variations, that no results by this method are included.

The following series of tests has been carried out to compare more directly the advantages of two of the frog-heart methods of digitalis assay previously mentioned. The minimum dose of each preparation was determined according to both methods under as nearly similar conditions as possible. By personal observation as to the definiteness of the end-point, we were able to form an opinion regarding the value of each method as a means of determining the activity of preparations of the digitalis series:

Table No. I.

FLUID EXTRACT DIGITALIS.

Description		M. L. D. 12-Hr. Method	Ratio, dose by 12-Hr. Meth. to 1-Hr. Method	Dose 1-Hr. Method
	1	.0010	(1.42)	.0007
	2	.0011	(1.37)	.0008
	3	.0017	(1.13)	.0015
	4	.0014	(1.55)	.0009
	5	.0016	(1.07)	.0015
	6	.0008	(1.14)	.0007
	7	.0008	(1)	.0008
	8	.0010	(1)	.0010
	9	.0008	(1)	.0008
	10	.0007	(1)	.0007
	11	.0009	(1.12)	.0008
	12	.0020	(1.81)	.0011
	13	.0013	(1.3)	.0010
	14	.0009	(1.29)	.0007
		Average	(1.22)	

Table No. II.

TINCTURE DIGITALIS.

		M. L. D. per gm. 12-Hr. Method	Ratio of Doses	1-Hr. Method Dose
U. S. P.	1	.014	(1.27)	.011
B. P.	2	.009 (.010)+	(1.5)	.006 (.007)
		Figured to U. S. P Strength		
B. P.	3	.010 (.011)+	(1.43)	.007 (.008)
U. S. P.	4	.011	(1.27)	.008
U. S. P.	5	.016	(1.23)	.013
U. S. P.	6	.012	(1.5)	.008
U. S. P.	7	.009	(1.28)	.007
U. S. P.	8	.009	(1.5)	.006
U. S. P.	9	.008	(1.6)	.005
U. S. P.	10	.016	(1.33)	.012
U. S. P.	11	.014	(1.4)	.010
U. S. P.	12	.005	(1.2)	.005
		Average	(1.36)	

Table No. III.

POWDERED EXTRACT

	1	.00024	(1.09)	.00022
	2	.00014	(1.4)	.00010
	3	.00030	(1.2)	.00030
	4	.00025	(1.25)	.00020
		Average	(1.20)	

PILL EXTRACT

	1	.00014	(1.27)	.00011
	2	.00018	(1.28)	.00014
	3	.00036	(1.28)	.00028
	4	.00036	(1.20)	.00030
	5	.00022	(1.22)	.00018
		Average	(1.24)	

	SCILLAREN-A AND DIGITALIN.		
1	.028	(1.33)	.021
2	.013	(1.41)	.008
3	.00009	(1)	.00009
4	.00004	(1)	.00004

TABLE No. IV.

STROPHANTHUS.

	M. L. D. 12-Hr. Meth.	Ratio of dose by 12-Hr. Meth. to 1-Hr. Method	1-Hr. Method
1	.00005	(.83)	.00006
2	.00004	(.80)	.00005
3	.00006	(.75)	.00008
4	.000045	(.32)	.00014
5	.00012	(.54)	.00022
6	.00011	(.64)	.00017
7	.00009	(.45)	.00020
8	.00007	(.43)	.00016
9	.00011	(.68)	.00016
10	.000075	(.53)	.00014
	Average	(.543)	

TABLE No. V.

SQUILL.

1	.0006	(.75)	.0008
2	.0007	(.87)	.0008
	Average	(.81)	

TABLE No. VI.

CONVALLARIA.

1	.00016	(1.23)	.00013
2	.00024	(1.09)	.00022
3	.00010	(.91)	.00011
	Average	(1.08)	

The fact which stands out most prominently from a superficial examination of this data is that the minimum dose of digitalis preparations is in most cases less by the one-hour method than it is by the twelve-hour method. The opposite is true in the case of strophanthus preparations. This seems more logical since one would naturally expect it to require more of the active substance to cause systolic stoppage of the heart in one hour than to cause the death of the frog. Digitalis in sub-lethal doses must, therefore, produce an early paralysis of the heart from which the frog recovers. This fact in itself would seem to point to a possible cause for discrepancies in the one-hour method.

It is only with samples of Tincture Digitalis that we are able

to obtain a clearly defined and uniform end-point by the one-hour method. In most of the tests of other members of the digitalis series the end-point is either difficult to determine because of inability to check the minimal dose or the heart does not stop in definite systole. It would seem that there should be some very nearly constant ratio between the minimum dose obtained by each method with the same preparation, but as stated above this has not been found true except approximately in the case of Tincture Digitalis.

Our observations would lead to the conclusion that the variability in the individual resistance of the frogs to digitalis plays a more important part in the one-hour method of assay than it does in the twelve-hour method and consequently adds to the indefiniteness and inaccuracy of results by the former method. The time element also has an important bearing on the comparative results by the two methods. Where the time which elapses between the injection of the active material and the observation of the result is relatively short the effect of the same dose of the same preparation (and by the same dose we mean in proportion to weight) upon frogs of different resistance may be sufficient to produce conflicting results. On the other hand, in a method involving a longer period of observation where the death of the animal rather than a paralysis of the heart is the final end-point this difference of resistance does not play so important a part. It is true that even in the twelve-hour method the variation in the resistance of the test animals is an important factor, but it can be more easily and completely eliminated by this method than could be done in the case of the one-hour method, even if a similar procedure were applied, *i.e.*, elimination of the factor of resistance variation by the use of a large number of test animals and of a standard for comparison.

The point that we wish to emphasize, however, is that while variation in resistance can apparently be offset in both methods by the carrying along of a standard preparation of known strength, yet there seem to be varying degrees of paralysis of the heart and that this paralysis has no uniform relationship to the death of the test animal. In the data on F. E. Digitalis in some cases the minimum dose was the same by both methods, but the average lethal dose exceeded the one-hour dose by 22 per cent.

with a maximum variation of 81 per cent. In the case of Tincture Digitalis the variation ranges from 10 per cent to 60 per cent, the average excess required to kill the frogs over that necessary to cause systolic standstill being 33 per cent. Comparison of Strophanthus tinctures by the two methods shows that 54 per cent of the one-hour dose will kill the frog, Squill 80 per cent, Convallaria 108 per cent.

From our observations we, therefore, summarize as follows: First, that the end-point in the one-hour method is more indefinite and consequently more difficult to determine than that of the twelve-hour method; second, that the variation in resistance of the test animal is a source of much greater error in the accuracy of the shorter method than it is in the other; third, that an absolute end-point such as death is more satisfactory than one which may show so many degrees of variability.

Our conclusion is that the death of the frog with heart in systole is a more accurate and dependable end-point in the reaction than a similar stoppage of the heart observed at any time previous to the absolute death of the animal.

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THE GLANDS OF INTERNAL SECRETION AND THEIR IMPORTANCE AS THERAPEUTIC AGENTS.*

Carey Pratt McCord.

The animal body, it appears, manufactures its own drugs. These drugs are the derivatives of the glands of internal secretion. These substances elaborated by the secretory cells of these glands are discharged into the circulation and carried to the various parts of the body. There they react upon the tissues in a manner for the well-being of the body as a whole.

The glands of internal secretion regulate and correlate some of the body's most important physiologic functions and constitute efficient protective and defensive measures against disease. There are, influenced by the glands of internal secretion, such functions as ovulation, pregnancy, muscle tonus, vaso tonus, secondary sexual development, adiposity, skeletal growth, sugar metabolism—on through an extended list. Despite the complexity and intricacy of these manifold manifestations of internal secretory activity the balance is maintained, in health, in perfect harmony—that is, the glands regulate and control each other. This interrelation and interdependence of the glands of internal secretion have given rise to the term "internal secretory balance." Although these several glands are situated in the body widely apart from each other and have no visible connections one with the other, they constitute a unified system of glands, every individual of which having its function or functions, but contributing to the maintenance of a complex interrelation within the entire system. It is now established that there exists not only an organic and functional harmony between all glands but a compensatory interaction as well. Every gland acts, in its peculiar functional manner, upon the blood passing through its tissues, often adding to it bodies of vital importance to the welfare of the individual. If any organic disease or abnormality exists in a particular gland, the missing or altered function appears in some cases to be taken over by some other gland, and disaster is

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prevented. In other cases the altered metabolism of one gland upsets the normal metabolism of all the others and leads to its impairment and the impairment of the body as a whole. In its deepest significance, it is probable that every cell in the body is a potential ductless gland and has some slight influence on the life and functions of its fellow cells. The terms "ductless gland," "gland of internal secretion" and "endocrinous gland," are, however, restricted to those organs showing glandular tissue and yet having no ducts for discharging the formulated substances.

The tissues producing internal secretions are, pituitary, pineal, thyroid, thymus, parathyroid, pancreas, adrenal, ovaries, testes. There are, in addition, some indications of internal secretion from the tonsils, placenta, and carotid gland.

Glands of Internal Secretion and Disease:—While the ductless glands functionate for the maintenance of the normality of the body, they themselves are subject to disease and traumatism. In many instances, apparently as a prevention against traumatism, the ductless glands are so located that the very shielded and privileged situation of these organs suggests a vital importance. The pituitary gland resting in the saddle of the *sella turcica* of the sphenoid bone at the center of the skull is the best protected organ of the body. Scarcely less protected is the pineal gland near the center of the brain, the parathyroids embedded in and behind the thyroid gland deep in the neck, or the adrenals padded in the fat above the kidney. The removal of the glands experimentally, by accident, or through necessary operative procedures, manifests the absence of the gland by distressing and even fatal symptoms. The removal of the adrenals, for example, leads rapidly to the death of the animal or patient with great prostration and depletion before death, due to the loss of the adrenal function of maintaining muscle and vascular tonus. The removal of the parathyroids leads to death from the accumulation of toxic bodies in the circulation, the destroying of which is the parathyroid's function. The removal of the pancreas leads to diabetes and later to death. Not all glands, however, are immediately essential to life. In adult life the testes, ovaries or pineal gland may be removed without producing fatal results.

It is not necessary that there be a visible anatomical destruction of the ductless gland to produce a perversion of its secretion

and thus a disturbance of the body's equilibrium. They are subject to tuberculosis, to cancer, to infectious diseases, that may lead to a slight or grave impairment, which may manifest itself as an increased or a decreased function. Increased function of the pituitary gland leads to gigantism, acromegaly, while decreased function produces obesity. Increased function of the thyroid causes goitre, while decreased function causes the coarse featured obese cases called "myxedema," and in young children is termed "cretinism." Even so mild a condition as the so-called "spring fever" may be a condition of decreased adrenal function. All considered, it is very evident that malfunction of these glands may produce very severe pathological states of the body, and it becomes a pertinent matter to inquire as to the efficacy of treating such conditions with preparations of glands derived from cattle, sheep, or other animals.

Ductless Glands as Therapeutic Agents:—The conception of using animal derivatives in treatment is by no means new. As early as 600 B. C. preparations from testes were given in the treatment of obesity. At about the same time there are also mentioned the use of such other animal substances as "swine's fat, dog's dung, fat of a serpent, hair of a virgin goat, and human bone." It is only a step from this to our present-day desiccated *corpus luteum* and pituitary extracts. It is, however, a far cry from the ancient to the modern point of view regarding such substances. The ancients used these agents, calculating that their vile tastes and nasty odors would drive away the offending disease, while, by us, organ derivatives are employed from our knowing that chemical substances are elaborated and stored by the organs and when given off into the circulation promote the welfare of the body organism. This rational use of glandular derivatives is only 25 years old, but, in these comparatively few elapsing years, a vast amount of work has been performed by scientific workers everywhere, until to-day we are confronted by a bewildering literature filled with contradictions, over-exploitations, speculations and theories, but, fortunately, here and there we find a clear-cut, undoubted fact that stands as a monument of human achievement.

Unrestrained speculation from the very incipiency of organotherapy has attached stigma to this form of treatment. There

has always been the over-optimistic type of worker who has held out greater virtues, as the properties of certain glands, than really existed as facts. Extravagant claims have actually retarded the fuller understanding of the possibilities and limitations of glandular therapy. So, let us recognize that we are surrounded both by existing limitations and by ignorance as to possibilities. Let us at once learn not to expect any panacea that will rejuvenate old men, or which will defer old age beyond a certain physiologic limit, nor can hopelessly anatomically defective minds be brought up to par. On the other hand, nearly every gland has its field of application. In many cases the application is specific, and neglect to use glandular tissue approaches criminality. Persistence in the treatment on the part of the physician is essential. Most of the glands, apart from such products as adrenalin and pituitrin, act so as to alter the metabolism. Such changes do not occur at once. For instance, no good results are to be expected from placing a mentally defective child on pineal medication for two weeks. Such treatment must be continued for months and even years.

One of the sources of error accountable for poor results may be ascribed to the chemical manipulation of glandular substances, with the desire to purify them and ultimately to obtain the active constituent in crystalline form. A chemically pure substance, active and freed from attending deleterious qualities due to contamination, is, of course, very desirable, but many glandular products are not standardizable and a mechanically nice-appearing product may be attained at a sacrifice of activity. Except in a few instances, adherence to a product closely simulating the original tissue is attended with better results, in the absence of any direct data regarding the nature of the substance stimulating the changes. This is especially true of such obtuse agents as the anterior lobe of the pituitary gland and the pineal body.

Very few of the hormones have been isolated in crystalline form, so that, for the most part, the properties of these hormones of the different glands are but meagerly understood. In general, they are the chemical means of correlation of the activities of the different parts of the body. They promote or moderate metabolism. In addition, special functions are attributed to some. Even with so vague a knowledge of the nature and properties of hormones, it is possible to indicate some lines on which with

safety we may proceed in the application of these glandular derivatives. They are likely to prove useful in five different ways:

1. The most obvious and natural use is in the treatment of the diseases due to destructive lesions of the glands by which the hormones are secreted. In this substitution treatment glandular derivatives are used in a sound and rational manner. Typical of this use is the employment of *corpus luteum* or ovarian extract in the treatment of artificial menopause due to the removal of the ovaries.

2. Glandular derivatives are serviceable when there is bodily demand for more secretion than the gland supplies. For example, the simple parenchymatous goiter of young women is due to overgrowth of the gland in its effort to supply a greater amount of the thyroid secretion. When such patients are placed upon thyroid medication, these simple goiters in many cases disappear.

3. The derivatives of one gland may be substituted in a deficiency of activity in another gland. For example, where osteomalacia is present and attributable to ovarian malfunction adrenalin preparations are many times useful.

4. A large number of conditions exist where glandular products are beneficial, but no connection is established between the pathologic condition and the gland function. Such may be called the "empiric use" of glandular derivatives.

5. The use of these glandular derivatives as drugs, for example pituitary extracts as an oxytoxic, or adrenalin as a hemostatic.

In the foregoing pages I have tried to make clear the importance of the glands of internal secretion in health and normal function, the possibility of disaster that may come to the body through perversion of secretory function from disease or traumatism, and, in the last paragraph above, it has been my desire to point out the rationality of combating disease and aiding normal functions by the administration of preparations of these glands. Since the cells of the various organs may be influenced in their functioning by substances procured from other animals, the possibilities at once opened up are immense. Progress to the ultimate control of many complicated conditions is limited only

by the capabilities of the scientific workers to produce satisfactory preparations of established and uniform activity.

This is an all too brief outline of hormone therapy to-day. New pathways in this field of therapy are opening up yearly. The principle of hormone therapy explains in many respects the action of the older drugs and affords solid groundwork for future methods of treatment. For these reasons I commend the glands of internal secretion to your further interest and study.

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CANNABIS SATIVA:*

Is the Medicinal Value Found Only in the Indian Grown Drug?

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(From the Research Laboratory of Parke, Davis & Co.)

Not many students of the subject will to-day answer this question in the affirmative. There is too much evidence to the contrary. Some, however, have not yet been brought to the point of accepting as "Standard," an extract of Cannabis Sativa irrespective of the locality from which the crude drug was obtained if the fact is noted that it is not of Indian origin. For this, undoubtedly, tradition is largely responsible. Originally only three or four provinces[1] on the west coast of India were included in the territory from which official, medicinally active hemp could be obtained. Later,[2] however, no limit was placed on the drug specifications except that it be from India; and as no distinguishing feature is present to assure its origin as being Indian, no doubt much material appears on the market from other sources and is accepted as "Indian."

This statement might be accepted as the cause for the uncertain action of the drug noted by many observers. What seems much more likely to be the reason for the inconstant and inconsistent results reported by some observers, is that the variable effects, both clinical and pharmacological, which are obtainable even with active material had not, at that time, been sufficiently recognized (Houghton[3]).

While the dog is generally accepted as the most satisfactory test animal,[1, 4 & 5] not every one is applicable for the purpose. Many of them must be rejected as not being sufficiently susceptible, and even the susceptible ones are not uniformly so.

This being true, unless exceptional care is exercised in observing the pharmacological action of the drug extract, misleading reports are certain to follow.

*Read before the Scientific Section at the Sixty-second Annual Convention at Detroit, Mich.

It is not the intention of the writer at this time to adduce data to prove the activity of American grown Cannabis Sativa, because it is possible to prove almost anything one wants to prove about the activity or inactivity of extracts of hemp. The intention is rather to point out the possible reasons for such contradictory reports as have been published. These are the result of incomplete or inaccurate observations, non-susceptibility of the test animal or patient, use of an extract whose activity had been destroyed, or the use of extracts from inert or only slightly active drugs. On the other hand, not infrequently a patient or a test animal is highly susceptible, and a particular sample of only average quality is reputed to possess exceptional activity. Many statements regarding the activity of hemp extracts are apparently colored by tradition, it being concluded without further comment that only the Indian grown drug contains the narcotic principle. Cushny[6] states that Cannabis Sativa is of pharmacological interest only when grown in warm climates, including Southern United States. Kobert[7] claims that the official preparations have no action on animals and that their action on humans is inconstant. Fraenkel[1] says: "The action of haschish differs greatly according to climate, race and individuality." Bibra's book[8] contains very interesting descriptions of experiments with haschish on humans which proved its strongly differing action on the individual. Sollmann[9] says: "Hemp grown in western countries is generally devoid of Cannabinol and is inactive." Wood (Geo. B.)[10] noted that the European hemp appeared to have none of the exudate typical of the Indian grown drug and of that growing in the vicinity of Philadelphia. If this last statement is true, it is a logical explanation of European opinion that only the drug from India contains appreciable activity. It is probably true only in exceptional cases. Wood (H. C.)[10] found that less than 1 grain of an alcoholic extract of Kentucky grown hemp was effective on himself. This would apparently indicate exceptional activity since 1 grain of Ext. Cannabis Indica will not ordinarily produce so intense an action as that described. Actually, it would seem probable that he is occasionally, or generally, more susceptible than the average person.

The most recent reference of note is that by Eckler and Miller[5] in which several series of experiments were carried out,

all leading to the conclusion "that if American Cannabis is made official, difficulty will generally be experienced in obtaining highly active lots which will compare favorably with a good Indian drug." One statement in their summary is that "very little dependence can be placed on the estimation of the extractive matter yielded to alcohol." This, in the writer's experience, is too general a statement. The extract is rarely inactive. When an extract is entirely soluble in cold 95% ethyl alcohol, the yield is a fair indication of the activity of the drug.[11] There are exceptions to this statement, however, so that it cannot be taken as true in any particular case without being verified by pharmacological assay, but it may be taken as roughly indicating the value, other things being equal.

The Powdered Extract Cannabis Sativa, from whatever source the drug originated, very readily deteriorates. In fact, one lot came under the writer's observation in which no activity could be detected, while the extract from which it was made was of full standard activity, *i.e.*, 10 mg. per kilo administered to a susceptible dog elicited the incoördination characteristic of the drug's action.[11] Undoubtedly, a similar deterioration may take place in the drug or in an extract without any recognizable change in its physical properties.

Exception may also be taken to the experiments of Eckler and Miller on account of the quality of the drug used. In no case was the quality of the crude drug at all comparable to the quality of the Indian Cannabis with which its activity was compared. A sample of crude drug containing a large proportion of seeds, stems, and leaves, this being the description applying to most of the samples they tested, is very different from the average quality of Indian drug imported, and one should not expect equality either in yield or activity. Much better drug should be and is available on the market.

The writer[11] has carried out tests for the activity of samples of drug grown personally from seed collected from Indian drug, and invariably found no activity in either the stems or seed. The leaves, however, when gathered before any brown color due to decay was evident, were found to contain almost as much extractive with almost the same activity as the imported drug which meets U. S. P. requirements, while the flowering tops of the

pistillate plant—the part corresponding exactly to the requirements for Indian Cannabis—were found fully equal and in some cases superior to the average good quality imported drug meeting U. S. P. requirements. This and other equally favorable results were reported in former papers.

There are occasional samples of American drug decidedly less active than standard both as regards yield of extract and its activity. These, however, can be paralleled by samples of Indian drug having no greater activity.

With the exercise of caution in selecting the drug and insistence on certain qualities essential to drug of good quality, American producers can supply material practically of equal value to that imported. It will be necessary, however, for manufacturers of extracts of this drug to recognize the economic difficulties that stand in the way of duplicating the physical qualities of the imported drug. Hand-picking is out of the question, and almost of necessity the commercial drug will contain leaves, stems and seeds with some admixture of the male plant.

To obviate the difficulty of so specifying as to exclude undesirable parts, it seems advisable to specify merely as regards yield and activity of extract from the botanically correct drug. Then, no sample of hemp plant that can be economically extracted and that yields an active extract, need be rejected because of physical difference from rigid U. S. P. specifications. If the extract is active and if the yield and the cost of the drug are compensatory we then have an economic condition that should be satisfactory.

Also as Scoville[12] has pointed out, the crude drug is not used as such and really requires no specifications except botanical.

Another question has been raised relative to the comparability of therapeutic and pharmacologic activity. This point was raised by Dr. Rusby and was answered in a paper presented before this section two years ago.[13] Experiments indicate that the dog, under rigidly prescribed conditions, is a satisfactory test animal and that lack of therapeutic results from pharmacologically active samples may safely be ascribed to individual variability. Schroof,[14] moreover, has pointed out that non-susceptibility is not absolute but is merely a question of quantity.

We conclude, therefore, that, first, American hemp contains the active constituent; second, if equal care is exercised in select-

ing the proper part of the drug for extraction, no material difference in activity will be found between extracts of Indian and American hemp; third, apparent lack of activity and variability in activity applies equally to both varieties of this drug; fourth, under proper direction there is no valid reason why American hemp cannot be collected to advantage to replace the imported article.

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The present system of collecting reprints of articles published from the Research Laboratory was begun in 1912. Reprints of the following articles published subsequent to that time are available and will be sent upon request. The publications marked (*) are no longer available.

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THE PINEAL GLAND.

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INTRODUCTION.

The animal body is controlled by an interlocking directorate. This directorate is made up of the glands of internal secretion. The derivatives of these glands regulate and correlate many of the body's functions and protective measures. Their influence is exerted on resistance to infections and intoxications, on nutrition and organic metabolism, on growth and decadence, on intellectuality and temperament. To this directorate the pineal body is but guardedly admitted by some and by others is flatly rejected as insignificant as an organ of internal secretion. Recent investigators would attribute to the pineal body functions heretofore hidden in the obscurity that to some extent still surrounds the ductless glands and their functions. As knowledge extends regarding this vestigial organ, its metamorphosis is a noteworthy thing. What is now the pineal body (pineal gland, epiphysis, conarium) was probably in earlier evolutionary stages a parietal eye or pair of eyes. As environmental conditions were altered, it ceased to functionate and lost all connection with the visual mechanism of the brain. Only in a few species of lizards does this organ approach functional activity. In the embryonic state of these animals distinct lenticular and retinal areas may be observed. In higher animal life, at the present time, the most suggestive indication of an earlier ocular function of the pineal is the melanopigment found in abundance in many pineal glands. This is probably a vestige of what in an earlier time corresponded to the choroidal coat of the present eyes. Although the pineal is no longer of use as a visual organ, it cannot be said to be merely a rudimentary body or vestige such as Starling describes when he wrote "the pineal gland has, as far as we know, no functions in metabolism. It is interesting as a vestigial remnant of a primitive dorsal eye." To the contrary, evidence is accumulating that is indicative of a marked influence exerted by the pineal gland upon somatic, mental and sexual development.

It is the purpose of the present paper to group together the essentials of the literature bearing upon this organ. It is not an exhaustive, critical paper, and as far as feasible the technicalities of the various investigations have been omitted.*

ANATOMY AND HISTOLOGY.

The pineal gland is situated in the brain just beneath the splenium of the corpus callosum. In the human its shape is nearly trilateral. The base is anterior and directed forward over the third ventricle. The base is attached to the habenular commissure and to the posterior commissure overlying the entrance into the Sylvian aqueduct. Between the habenular and posterior commissures a small pointed diverticulum, the pineal recess, extends from the third ventricle for a very short distance into the pineal body, and thus recalls the early condition in which the organ is developed as a tubular outgrowth in the roof plate of the diencephalon (Piersol). The apex of the gland extends backward and downward and is suspended between the anterior quadrigeminate bodies.

Bailey and Jelliffe,[1] in summing up the anatomy of the pineal gland, point out its significance as a causative factor in intracranial pathology. "It thus lies close to the communications between the third and fourth ventricles, to the cerebellar and pontine spaces, and is in direct contact with the large venous channels that drain the central region of the brain. Hence, in enlargements of the pineal, circulatory disturbances will develop first, with the formation of varying degrees of hydrocephalus. Often the hydrops develops with great rapidity, though it may do so very slowly, and is undoubtedly conditioned by at least two independent factors—namely, pressure on the veins of Galen, and obstruction to the aqueduct of Sylvius. Then again, there are reasons for believing that growths in this region further stimulate the production of cerebrospinal fluid, in which case an additional factor for hydrocephalus development comes into consideration."

* [illegible] recently used the review published by Kidd in the *Medical Chronicle*, December, 1912. This is an exhaustive paper and embraces many phases of study of the pineal gland that the scope of the present paper does not permit. It is especially thorough in its review of studies upon the pineal's anatomy and histology.

Histological studies have in the main been prosecuted toward establishing (1) the presence of glandular tissue; (2) the presence of contractile tissue supporting the view that the gland is a valve regulating the flow of cerebrospinal fluid; (3) nerve fibre communication between this gland and other parts of the brain; (4) evidence of involution changes in the gland indicating a cessation of function.

It would appear that there is acceptable evidence of the glandular nature of the pineal. It is to be admitted that the glandular elements are scant and ill defined. Beidl's[2] description of the pineal's histology is essentially that of glandular organs. "In newborn infants the pineal gland consists of irregular lobes held together by a small quantity of connective-tissue; *the lobes are composed* of cells of almost the same type, but arranged irregularly, being crowded together in the interior of the organ. The pineal cells have a pale, tinted protoplasm and very characteristic nuclei, these being large and oval, and crowded, over their entire circumference, with granules. Dimitrowa distinguishes four different nucleus forms. Other important histological details are (1) the peculiar nature of the ependyma of the recessus pinealis, in which cubical epithelium and epithelium composed of goblet-like cylindrical cells alternate; and (2) the cysts which are observed at the base and in the interior of the pineal gland of newborn infants, and which probably represent obliterated blood-vessels. The pineal gland shows signs of involution before the age of puberty, the first symptoms being observed in the seventh year. The concretions known as pineal sand or acervulus, which consist of calcium phosphate and calcium carbonate, are found in the glia layer which covers the commissura habenularum. As age increases, a distinct increase of the connective substance at the expense of the glandular tissue takes place. The glandular lobes are replaced by plaques composed of connective-tissue and a very fibrous glia tissue, and these plaques contain isolated glandular cells. The connective-tissue septa further undergo hyaline degeneration, and may completely calcify. Occasionally, homogeneous masses are observed in the septa or in the interior of the glandular lobes, and, after the deposition of calcium salts, corpora arenacea are evolved from them. The glandular cells also present signs of involution, but even in extreme old age

glandular cells are encountered which are intact and apparently still functionally active."

Jordan,[3] in 1911, published the results of his work on the histogenesis of the pineal gland of the sheep. He studied the gland at various stages from 2.5 c.cm. embryo to old sheep. Of the gland at full term he writes: "The specimens in hand lack about a week of full term. However, the pineal bodies are in all respects, except size and number of granules, like those of lambs (each eight months). They contain numerous alveoli of varying calibre and length, and considerable of the cells contain small amounts of melanic granules. The characteristic new feature here is the great abundance of follicular arrangements of cells about central vascular connective-tissue trabeculæ. Since all of the features of the adult pineal gland are here present and in less complicated form, it seems desirable to describe them more in detail.

"The body simulates a lobulated gland. The lobules are delimited more or less distinctly by coarser and finer rectilular septa or vascular connective-tissue continuous throughout, and peripherally, through the coarser trabeculæ, with the pia mater. The lobules consist of one or several follicular aggregations of cells. These are spherical or oval masses, the parenchyma of which consists of two distinct types of cells with several intermediate types. The framework of the parenchyma is a reticular structure of delicate neuroglia fibres, for the most part continuous with the irregularly polygonal and flattened stellate neuroglia cells. Many of the coarser fibres seem entirely free from the cells, as in typical neuroglia tissue. The second main type of cell, oval and spheroidal or polyhedral, occupies the interstices of the neuroglia meshwork. Many of the cells still contain numerous melanic granules, more especially peripherally and in the walls of the alveoli or cysts. The latter are still abundant and quite large.

"A conspicuous feature is the great vascularity of the pineal body. Frequently, capillaries terminate in the form of tangled loops or 'glomeruli' within spaces surrounded by more compact parenchyma. Such spaces in some cases represent alveoli into which a trabecula has carried blood-vessels. It remains to note that both the parenchymna and neuroglia fibres are more abundant peripherally. The latter also are coarser in this region. The entire body, exclusive of the vascular pial trabeculæ and a few

white nerve fibres, is composed of more highly differentiated or interneuroglia cells of the original ependyma of the third ventricle."

Cajal,[4] in 1895, demonstrated sympathetic nerve fibres in the pineal. The axons form a plexus in the vicinity of the glandular cells, but the terminal nerve twigs do not penetrate the cell protoplasm. This is the nerve fibre and gland cell relation in other secreting organs. Polvani,[5] in 1913, basing his deductions on the histological study of the human pineal gland, at various periods of development, denies that this organ is of a nervous or lymphatic nature; he admits the existence of neuroglia tissue, but he attributes to it only a secondary importance, relative to the principal cells in which he recognizes the glandular character. The gland nature of the pineal is denied by many of the earlier modern writers. There are adherents to the belief that the organ is only a lymph ganglion; others that it is pure neuroglia, etc.

The occurrence of muscle fibres in the pineal body would attach significance to the valve action of the pineal in regulating the flow of fluid through the aqueduct. Nicolas[6] found striped muscle fibres in the pineal from cattle. These fibres are few and scattered. Dimitrowa[7] confirmed this finding, but otherwise there has been no substantiation of this. Illing,[8] in 1910, reported the occurrence of non-striated muscle fibres in cattle, but Jordan, in 1911, was unable to find either striated or non-striated fibres. So also Funkquist,[9] in 1912, failed to find muscle fibres in the pineals from hen, duck, diver, canary, sparrow, ox, pig, rabbit, rat, hedgehog, cat. This writer is of the opinion that the muscle fibres described by others are only "myoid" forms of neuroglia.

In such reptile forms as have a pineal body retaining in some measure its original function, well-defined nerve fibres are demonstrable. In the human, according to Piersol, apart from a few nerve filaments in the anterior part, probably sympathetic in origin and destined for blood-vessels, and a dense network of neuroglia fibres, the gland contains no nerve elements.

As early as 1854, Faivre[10] recognized that the gland in childhood and in adult life is histologically different. Involution changes are attested to by workers both in animals and in humans. In children (Krabbe) the gland attains to its greatest activity by the seventh year. From that time on, involution changes are dis-

cernible. These retrograde signs are described by Krabbe as connective-tissue proliferations, concretions, cysts, neuroglial plaques, cells of disintegration. The gland is, however, very stable, and this lends significance to a function for the adult gland. The involution signs at ninety-two are no more pronounced than at fourteen. In only one case did this investigator find complete degeneration. From his histological studies he is inclined to believe that in adult life the gland functionates.

Jordan's paper, dealing as it does with successive stages of the sheep's pineal, indicates these degenerative signs: "Pineal bodies of sheep of the third year are characterized by several degenerative changes, viz., (1) great increase in the connective-tissue elements; (2) large and numerous areas of dense neuroglia network free of cells; (3) areas of apparently coagulated fluid matter; (4) large clumps of intercellular pigment granules in the peripheral portion; (5) comparative rarity of spherical interneuroglia cells. The histological characteristics point to a cessation of active function and to the onset of degeneration. Judging from the standpoint of histological and cytological features, the assumed specific function of the pineal gland is important, perhaps essential, only during the first year of life."

Summary.—Cytological studies, prosecuted under the best conditions and extending over successive stages of development in several species, lend support to the contention that the pineal body is glandular in its nature. The gland elements are few and ill defined. Neuroglia and nerve fibres are to be found at least in certain animals, but these are probably of secondary importance. The gland undergoes involution changes, beginning in the human as early as the seventh year. The degeneration is not complete, and the histological picture of the adult gland is not such as to remove the possibility of a physiological function of the gland in adult life.

EXTIRPATION EXPERIMENTS.

In the study of the pineal body's functions, the changes concomitant to the gland's removal have frequently been under observation. No other gland is removed with so great difficulty. Attempts to remove the gland have been frequent, but injury to the vermis or occipital lobes, or hemorrhage from the venous sinuses, has led to death of the animals in by far the greater num-

ber of instances. By operating on a large number of animals, several workers have had a few animals survive the severe traumatic procedures. Growing out of these studies a number of papers are available describing the technique of pineal extirpation and the function of the gland as manifested in changes following the gland's removal. Unfortunately, the findings from the several investigations are by no means in harmony. A complexity of factors contributes to this divergence of opinion. Among these vitiating factors, interfering with the proper interpretations of results due purely to pineal removal, are, first, body changes due to the severe operative process necessary for the gland's removal; second, the comparison of results obtained from adult animals with those from young animals; third, on incomplete removal of the gland, inflammatory changes in the remaining functional part may increase the secretion of the pineal substances. Results from the experimental extirpation of the gland should lead to the answering of such questions as (1) Is the operative removal of the pineal gland in animals feasible? (2) Is the entire gland or a part essential to life? (3) What immediate changes occur on its removal? (4) If not essential to life, what remote changes occur, such as alterations in the general metabolism or disturbances in the other endocrinous organs?

Our knowledge regarding such phases of pineal functions as may be determined by extirpation is largely based on the papers here briefly reviewed.

In 1910, Sarteschi[11] attempted the destruction of the pineal with the cautery. The animals employed were rabbits, and no changes followed the application of the cautery to the gland. Likewise, Exner and Boese[12] applied this method in part of their experiments on rabbits and likewise obtained negative results. In some of Sarteschi's rabbits the gland was removed with the knife. Only two of these animals survived. They became much emaciated, and although in pens with males they did not become pregnant. This worker, in 1913,[13] however, reports the production of the macro-genito-somatic syndrome in young rabbits and puppies. Inasmuch as the original paper is not available to the present writer, an abstract by Kidd is in part here used.

Sarteschi has now obtained this syndrome (precocious macro-genito-somatic) by experimental pinealectomy in very young rab-

bits and puppies, as Foa did in cockerels. Sarteschi attempted it also in very young kittens, but with constantly fatal results. He used the operative procedure of Lo Monaco—namely, ligature. This obviates the risk of hemorrhage. A temporary ligature of the carotid artery gives an anemic field of operation. Out of 23 rabbits operated on at the age of about forty-five days, 3 only survived; a small remnant of the pineal body was found on autopsy, and the testes were greatly hypertrophied, as in Foa's cockerels. The rabbits had, up to the time of their death (at the age of five to seven months), grown much more than the controls of their own age. All the organs and internal secretory glands were normal. Sarteschi concludes that in rabbits pinealectomy, whether it be complete or incomplete, determines a great bodily development, sexual precocity, and a notable enlargement of the testes. In puppies the operation is more difficult; out of 27, only 5 survived. Operation took place at the age of two months. Substantially the same results followed as in the rabbits. The testes of one puppy were of adult size before he was five months old; on autopsy they were histologically normal. Another male puppy showed, at the age of five months, great size and adiposity and enlarged testes. In conclusion, Sarteschi accepts Pellizzi's hypothesis that the pineal body exercises a moderating action on genito-somatic development.

Foa, in 1912,[14] after extensive preliminary work, from which he decides that the rabbit is wholly unsuited for pinealectomy, directs his attention to pinealectomy in young chicks and reports the production of precocity in body and sexual developments in young cocks. The glands were removed from the chicks at about one month of age. The mortality percentage was very high, only 25 per cent. of his animals surviving. The females of the series evinced no indications of any changes due to pinealectomy except the retardation in growth during the first two or three months subsequent to the removal of the gland. The three young cocks, according to Foa, after eight to eleven months, showed excessive growths of combs and testes and exhibited indications of greater sexual activity. Although the number of animals under observation in this work is small, the communication is a valuable one and represents careful insight into the problems of the experimental study of the pineal gland.

The most recent publication relative to extirpation experiments is another by Foa.[15] These new experiments upon chicks and rats are reported by Foa to substantiate his earlier claims as to the pineal's functions. He thus summarized this recent work: "The new experiments on the extirpation of the pineal gland in the young male chick confirm the result which I previously obtained, that the operation is followed by a development of the testes and the crest greater than in the non-operated control cock. The difference begins to manifest itself five months after the operation and increases constantly up to the ninth month. The operation produces no effect on the general development of the body in the fowl.

"The extirpation of the pineal gland, in the very young rat, produces no appreciable effect in the female; in the male it provokes a more rapid somatic development and the maximum difference is observed, between the weight of the operated animals and the controls, twenty-six to thirty days after the operation. Then the weight of the operated animal gradually becomes equal to that of the control.

"At the moment when the difference in weight reaches the maximum, one observes also a markedly greater development of testicles in the operated animal. The difference in the testicles disappears when the weight of the body becomes equal.

"The histologic examination of the testes, in the cock as well as in the rat, at the time of maximum difference in volume, reveals a uniform development very advanced in all of the tissues of the gland; the diameter of the canaliculus is increased, the opening enlarged; the mass of spermatozoa which fills the canalicular opening is greater; the canaliculi are more separated from each other and consequently the interstitial tissue shows greater development. [illegible]e is no difference in the spermatogenetic process, if one excepts the quantity of spermatozoa which fills the larger opening of the canaliculus.

"The canalicular tissue and the interstitial cells being uniformly more developed in the operated animal, it is impossible to say that to any of these tissues is due the greater development of the secondary sexual character in the cock and the somatic development in the rat.

"The experiments on the rats have shown that the extirpation

of the pineal gland does not determine an absolute hypertrophy of the testes, but a premature development of them. Forty-eight days after the operation, the operated rat cannot be distinguished from the control. This observation confirms the theory which attributes to the pineal gland an inhibiting function in the sexual development; we learn from this that with the beginning of puberty there coincides an involution of the pineal gland."

Dandy[16] is cited by Cushing as having removed the gland from dogs. The age, whether puppies or adults, is not stated. No recognizable changes attended the gland's removal.

Biedl writes in regard to his work in removal of the pineal gland: "I have occupied myself for some time with experiments, the main object of which has been to determine the clinical results of pineal suppression. I have succeeded, so far, in extirpating the pineal gland by a method similar to that which I employed in hypophysectomy. As far as my observations go, the pineal gland in the adult animal is a negligible quantity; my experiments with young animals are not as yet complete."

Summary.—Some of the questions asked in the preceding paragraphs are now answered by the work just cited. The removal of the gland is surgically possible. In experimental work this frequently has been done, but the trauma is great and death occurs in a large majority of cases. The removal of the gland in clinical cases, while possible, is attended with severe risk and is not to be considered as a probable form of treatment under any except unusual circumstances. The gland is not necessary for the maintenance of life. The early symptoms ensuing after operation are probably concomitant to the traumatism. No changes attend the removal of the gland in adult animals. As to the effects of removal of the gland in young animals, some dispute has arisen. Sarteschi and Foa respectively state that the gland's ablation leads to precocity of development. Certainly no experimental results are so complete as to allow comparison with the very striking syndrome seen clinically.

CARDIOVASCULAR STUDIES.

Studies of the relations between the circulatory system and endocrinous glands have yielded instructive and valuable results bearing upon the nature of the derivatives of several of the

glands, notably the adrenals. Such studies carried out with pineal extracts have led to contradictory conclusions in some respects. For the greater part, the results are of physiological interest rather than of utilitarian importance. Howell,[17] in 1898, was the first to make intravenous injections. A few injections of pineal extracts were made as controls in experiments upon the action of pituitary extracts. Apparently no significance was attached to these experiments by Howell. Von Cyon,[18] in 1903, using rabbits as subjects, made a study of pineal extracts. This worker reports that extracts are without demonstrable effect upon the blood-pressure. With small doses he obtained a rapid and feeble pulse which he attributes to the presence of inorganic salts in the gland. At the time of this publication, von Cyon concluded that the pineal function was purely a mechanical one serving to control the flow of cerebrospinal fluid through the aqueduct. Dixon and Halliburton,[19] in 1909, in their experiments of this type employed a preparation of desiccated sheep pineal gland. The dried glands were extracted with various reagents and injected intravenously into cats. Very small doses were employed, and with such small doses but scant alterations in the cardiovascular system were observable. Although a transient fall in pressure of blood occurred following their larger doses of this dilute extract, no charges are reported by them as occurring in the heart, respiration, intestinal volume and kidney volume. Ott and Scott,[20] in 1912, in several of their papers on internal secretion refer to experiments with pineal glands. Noteworthy are their observations that pineal extract induces vasodilatation in the erectile tissue of the generative organs of the male cat, stimulates the contraction of the intestinal wall and uterus, produces a diuresis and glycosuria, and increases the activity of the mammary gland.

By far the most exact study of cardiovascular changes subsequent to pineal extract administration has been made by Jordan and Eyster[23] in 1911. The material employed was sheep's pineal glands, either fresh or preserved in alcohol or formaldehyde. The amount constituting a dose was usually the extract from one gland given intravenously. Their own summary here appended gives the scope of their work and their conclusions:—

"Our experiments indicate that the pineal gland of the sheep

contains some substance (or substances) which, on intravenous injection in certain animals, cause a fall of blood-pressure associated with a vasodilatation in the intestines, produce a slight degree of the improvement in the beat of the isolated cat's heart, and cause a transitory diuresis associated with glycosuria in about 80 per cent. of the cases. We have found, in agreement with Dixon and Halliburton, that the effect on blood-pressure in the cat is small and unimportant. It should be noted that our extracts were in all cases more concentrated than those employed by these investigators. On the whole, our work would seem to indicate that while certain definite effects on the circulation and secretion of urine are produced in certain animals as the result of intravenous injections of extracts of the pineal body, the action is relatively slight when compared with that produced by extracts from other glands known to furnish internal secretions.

"Our experiments deal obviously only with a possible rôle of the pineal body in producing certain relatively rapid effects on the circulation, respiration, and secretion of urine. They leave entirely untouched the possibility of more gradual effects over longer periods of time, as well as the influence these bodies may exert on metabolism or other functions and their relation to other organs of internal secretion."

In Dana and Berkeley's[25] paper, 1913, which will be considered in further detail in the section on feeding experiments, reference is made to some cardiovascular studies. The following is a quotation summarizing their findings:—

"The blood-pressure experiments were virtually negative. Two dogs were used. The first dog received in rapid divided doses, intravenously, a concentrated solution of the nucleoproteid extract of 30 calves' glands. There was no response. The same animal then received intravenously 2 oz. of the globulin-albumin content of the same glands—without result. The second dog received a concentrated filtered saline solution of 24 bullocks' pineals, with no essential response."

The present writer has carried out 20 animal experiments in which pineal extract was intravenously injected into the jugular of dogs anesthetized with chloretone. The pineal extract was made up from fresh glands by grinding in a mortar with saline. The usual dose was one gland in 2 c.cm. of saline maintained at

body temperature. In striking contrast to the results just quoted above, some of our dogs were killed by a single injection of one gland in saline. The phenomena associated with the injection and subsequent effects were a rapid fall of blood-pressure, depressed and irregular heart, intense venous engorgement, death in from one-half to one minute. Smaller doses produced less intense results and many animals survived a dose of two or more glands prepared in the same manner as above. These cardiovascular changes occur equally intensely from glands from calves and from older cattle.

Summary.—The immediate results attending the intravenous administration of extracts from the pineal gland are not usually pronounced. Such phenomena as a decrease in arterial tension, dilatation of the blood-vessels, altered rate and amplitude of the heart-beat, diuresis, glycosuria, increased mammary secretion, have been reported and confirmed. The intensity of these several activities is so slight that up to the present time only techincal importance may be attached to these findings.

THE ADMINISTRATION OF PINEAL GLAND TISSUE.

Contrary to the current belief that the pineal gland functionates by holding in abeyance too rapid somatic, sexual and mental development in early life, are the recent experiments tending to show that feeding of pineal substance to young animals induces very similar changes. Observations have not been confined to animal experiments, for in cases of mental deficiency in children treatment with pineal gland substance has proved of value in increasing the intellectuality. In the animal experiments reported by Dana and Berkeley,[24] [25] and by McCord,[26] the noteworthy difference was in the rate of growth of body of pineal-fed animals over controls. It is remarkable how small an amount of pineal gland will, when administered orally, produce a more rapid growth of the body over controls, from the same litters or broods. So small an amount as 20 mgrm. weekly will stimulate growth beyond the normal rate. A large series of experiments aggregating 250 animals have uniformly shown the same result. The pineal-fed animals grew faster and were more resistant to infections. This growth was never beyond normal adult size. It was impossible to produce gigantism. In breeding experiments (Mc-

Cord) it was observed that the pineal-fed females gave birth to young earlier than their controls. This cannot be taken to mean that the gestation period was shortened, but apparently indicates that sexual maturity is attained earlier by the pineal-fed animals.

In a recent series of experiments (48 guinea-pigs) the present writer administered the pineal substance in sterile solution hypodermically. The glands for this material were removed from calves' brains under aseptic conditions. It was so prepared that 1 c.cm. represented 20 mgrm. of a fresh pineal gland. Of this, ½ and later 1 c.cm. constituted a dose. This was administered three times weekly. The controls were given in the same manner an equal amount of brain tissue. The body growth resulting was even greater than for oral administration. At the end of the first week the pineal animals had more than doubled the gain of the controls. Continuing this for six weeks, the average gain in excess of controls was 26 per cent.

It is not easy to draw the separating line sharply between the defective and the normal child. Between the normal child and the child hopelessly mentally deficient through gross anatomical anomalies, there exists a class so large as to embrace 1 per cent. of all children of school age in this country. As pointed out by Berkeley and others, there are no physical stigmata in the make-up of many of these children to indicate any defect. They are many times beautiful children, well proportioned, with well-shaped heads and limbs and normal eyes. The retardation that comes from adenoids and tonsils, although common in this class of children, can be ruled out in many cases. After the elimination of the cases attributable to such conditions as gross anatomical defects, adenoids and tonsils, hereditary syphilis, malnutrition, starvation, vicious environment, uncinariasis, etc., there remains a large number that to the trained mind of the teacher or medical observer may be characterized as "backward, dull, stupid." It becomes more and more evident that the glands of internal secretion are frequntly etiological factors in these disorders. McCready[27] emphasizes that not one gland but the entire system of glands is inefficient in these cases. He lays stress on the vitiating influence on embryonic development of tuberculosis, syphilis, cancer, chemical poisons, malaria, alcoholism, drug habits, insanity, goitre, malnutrition and various environmental conditions of

the progenitors. As a result, there appear the conditions of infantilism, degeneracy, hypoplasias, idiocy, etc., in varying degree. A more extensive review of the literature of this matter emphasizes the plausibility of attributing some of the types of mental deficiency to glandular irregularities. It will be found, however, that organotherapy has by no means been uniformly successful. In the hands of some, excellent results have followed the administration of polyglandular or monoglandular preparations.

Recent work has attached importance to the pineal gland as a stimulator of mental activity. The precocity of mental development found in some clinical cases of pineal tumors is sufficient to associate this gland with an influence upon mental activity. Dana and Berkeley, after a long period of preliminary experimentation as to dose, toxicity, etc., prescribed pineal gland substance for children of low grade mentality. Fifty children were so treated and these were carefully controlled with other children of the same age, sex and diagnosis; Binet tests were made the criterion of mental advancement. There was no immediate rapid body growth, but on continuing the treatment over a long period, the mental development was greater than prior to the treatment and in excess of controls of the same mental age. In individual cases, the results were striking. It is significant that only glands from young animals were active, and only in young children, below fifteen, were results obtained. This treatment has been repeated by others with good results. As to the mechanism of these changes, little can be said apart from speculation.

Summary.—The administration (orally or hypodermically) of pineal gland tissue is reported to induce development changes similar to those usually associated with pineal gland deficiency. In young animals the most pronounced effect of pineal administration is a rapid growth of body, but children of low mentality when treated with such material do not exhibit rapid body growth but do improve mentally. Only young children (up to twelve or fifteen years) are influenced by such treatment.

PINEAL NEOPLASMS AND RESULTING FUNCTIONAL DISTURBANCES.

Tumors of the pineal gland are not of frequent occurrence. The total number of authentic cases is not more than 70. These cases with subsequent necropsy findings have been the source of

the greatest amount of information as to the functions of the pineal gland. With tumors involving this organ two systems of signs and symptoms may be associated—the neurologic and the metabolic. These tumors may occur at any age of the patient, but the symptomatology varies with the age of the patient. In adults only the neurologic signs and symptoms occur. These are manifestations of encroachment upon the intracranial contents and are indications of changes in pressure, in position, and of destruction of tissue. In children, however, a second group of symptoms and signs may arise—the metabolic. Such changes are the outcome of disturbance in the gland's secretory function. This syndrome appears to be more complete in young males, but it cannot be said to be confined to young males. This syndrome due to perversion of pineal function consists, first, of early sexual maturity, evidenced in the enlarged sex organs, pubic hair, general body hair, early change in voice; second, precocious mental development evidenced in the maturity of thought and speech; third, general body overgrowth to the extent that a child of five or six years may have the appearance of a child of eleven or twelve. The syndrome is rarely complete, and all considered only about 10 per cent. of the 70 cases present metabolic changes that may be associated with pineal function. Inasmuch as this is not an exhaustive review, the very interesting case histories of these patients cannot here be included. A detailed and accurate review of the clinico-pathologic material may be found in the publication by Bailey and Jelliffe. Since the appearance of their paper a few new cases have been reported. The patients were adults manifesting no metabolic symptoms attributable to the pineal gland functions.

On perusing the cases cited in the available reviews, it is at once evident that the metabolic changes associated with functional activity of the gland are confined to prepuberal life. Many cases of pineal tumors below puberty manifest none of the signs of precocity of development that are so striking in a few selected cases. A study of the clinical material reveals how little consideration has been given to the possibility of pluriglandular involvement. In fact, in most cases the necropsy demonstration of a pineal tumor led to the association of all prior metabolic changes to pineal functional perversion. This grew out of the prevalent

conception of each endocrinous gland as an entirety entering into no interrelations with other similar organs. Judging these cases in the light of recent advances in pituitary pathology and physiology, it is difficult to delineate the manifestations of pure pineal derangement from the manifestations that almost inevitably must be connected with a pluriglandular condition. Cushing has pointed out that from the intracranial alterations attending pineal neoplasms, the hypophyseal functions are usually deflected from the normal.

Precocity of development when it does appear in tumor cases has long been attributed to deprivation of the body of the substances elaborated by the gland because of destruction of the gland by the neoplasm. As has been noted in the section on pineal extirpation, results from Foa and Sarteschi bear out this contention. These considerations led to the belief that the pineal gland functionates by holding in abeyance the rate of body growth, and the development of the mind, and of genital organs and functions. In some recent experimental work, which is reviewed in another section of this paper, a similar precocity of development from feeding pineal gland to young animals is reported. This unfortunately injects confusion into an already intricate situation. On the basis of ascribing precocity of development to pineal deficiency it would be anticipated that pineal feeding would lead to a retarded development and late maturity. The reverse was the actual outcome. It was found that administrations (orally or by hypodermic injections) of minute quantities (as little as 20 mgrm. weekly) led to rapid body development, early sexual maturity, enlarged testes, increased mentality. Out of this arises a very perplexing situation. It would appear that the experimental removal of the pineal gland or destructive tumor of the gland leads to the same results as does feeding or injecting the pineal material. The question arises, may the precocious macro-genito-somatic syndrome not be a manifestation of hyperpinealism rather than hypopinealism? In the publications by Marburg[28] and Polavani there is a tendency toward attributing to the pineal a constructive stimulating function. The former attributes all pineal adiposis to hyperpinealism and to him the true picture of apinealism is cachexia. The condition of cachexia in pineal tumor cases is of sufficient frequence to lend some sup-

port to the above contention. In cases of complete destruction of the pineal gland reported by Ogle, Nieden, Gowers, Massot, Nothnagel, Forster, cachexia, especially in the final stage, was the paramount sign of the condition. This cachexia is at times preceded by adiposis.

Polavani deprecates the findings from experimental extirpation of the gland. He points out the extreme difficulty of complete removal of the gland by operation. Contradictory findings at the hands of several workers may be due to the leaving behind of portions of the gland. Sarteschi reports that on autopsying his animals, subjected earlier to pineal extirpation, portions of the gland were found to have been left behind. In other work, the portion of the brain excised by operation has been sectioned and stained and has been found to represent the entire gland. While portions of the gland are undoubtedly left behind and under the whip of inflammatory processes may be unusually active, any wide generalizations are, in the presence of so few facts, unjustified.

In an effort to harmonize the production of similar changes by two opposing causes, the destruction of the pineal gland on the one hand and the administration of the gland substance on the other, there arise two possibilities worthy of further work. First, the precocious macro-genito-somatic syndrome may result from disturbing the general endocrinous balance either by increasing or decreasing the amount of pineal secretion available for the body's use. Bearing upon this is the writer's observation that feeding of pineal substance to male guinea-pigs leads to a hypertrophy of the testes with a microscopic picture similar in some respects to that recently described by Foa as occurring concomitant to glandular extirpation. Second, the cells of the neoplasms involving the pineal gland may retain some of the metabolic and other functional characteristics of the normal pineal cell from which they were derived, and the peculiar body, sexual and mental changes in patients with such tumors are all manifestations of increased rather than decreased pineal activity. There is abundant evidence that at times cells of tumors functionate after the manner of the cells from which they arise. In adenoma of the liver, in cases reported by Weber,[29] Rolleston,[30] Wheeler,[31] and Ribbert,[32] distinct bile secretion by tumor-cells has been

pointed out. Ribbert established that the bile present in such tumors was not the bile of icterus from necrotic liver-tissue by demonstrating that the scirrhous encapsulating tissue was free from bile stain and that the bile was confined to the liver-like cells of the active tumor. In at least one case, a metastasis in the lung from the liver secreted bile. In this connection it is significant that the functionating glandular cells of typical thyroid structure have been found in thyroid metastases in bone-tissue. Furthermore, in myeloma of the bone-marrow the cytoplasm[33] of the tumor cells contains the granules that characterize normal myelocytes, that is, the tumor to a certain extent assumes the function of the bone-marrow. All considered, it is perceived that functional activity of tumor-cells is not infrequent. Germane to the present contention is the statement of Hinds Howell[34] in describing the characteristics of the cells of the pineal tumors of his 3 cases. He says: "A noteworthy feature is the similarity of these tumor-cells in many instances to those of the normal pineal gland."

Summary.—Neoplasms of the pineal gland are rare and only a low percentage of authentic cases have shown the results of derangement of the gland's secretory functions. The precocious macro-genito-somatic syndrome is only found in the prepuberal age and is more complete in young males than in females.

Manifestations of unusual development in patients with pineal tumors have in most instances been attributed wholly to perversion of the pineal's functions. In the light of recent advances there are many indications of a pluriglandular involvement in some cases. Divergent findings in these cases are made more harmonious by considering the influence that other glands may exert in the production of the clinical picture. The hypophysis is very likely to become involved.

Whether neoplasms of the pineal retard (hypopinealism) or increase (hyperpinealism) functional activity, is a matter of divergent opinion. Experimental evidence is available, supporting either contention.

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REPRINTS OF PUBLICATIONS FROM THE RESEARCH LABORATORY, PARKE, DAVIS & CO., DETROIT, MICH.

The present system of collecting reprints of articles published from the Research Laboratory was begun in 1912. Reprints of the following articles published subsequent to that time are available and will be sent upon request. The publications marked (*) are no longer available.

1. On the Administration of Diphtheria Toxin in a Collodion Sac. By E. C. L. Miller. (*Journal of Infectious Diseases,* Vol. 8, January, 1911, pp. 50-65.)

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THE FILTERABILITY OF BACILLUS BRONCHISEPTICUS: WITH AN ARGUMENT FOR A UNIFORM METHOD OF FILTRATION.[1]

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In 1898 Nocard and Roux described a small polymorphic microörganism as the cause of contagious pleuropneumonia of cattle. This organism was found to pass through both Berkefeld and Pasteur candles. Since then several other organisms, both pathogenic and non-pathogenic, have been described as filter passers and demonstrated in the filtrate, some by their morphology, others by their pathogenicity.

The purpose of this paper is to place on record a series of filtration experiments with an easily recognizable bacillus described as the cause of canine distemper by Ferry (1910[2]), McGowan (1911[3]), and Torrey (1913[4]). The organism (*B. bronchisepticus*) varies in size from 2.3 *u* to 0.5 *u* in length by 0.5 *u* in diameter, is motile, stains readily with aniline dyes, is negative to Gram, and can be cultivated on all ordinary media.

Realizing that the bacillus in question is a very minute organism, the author determined to prove, if possible, its ability to pass through the pores of filters used for the demonstration of the presence of known filterable organisms. The only difficulty encountered was in finding a proper and satisfactory means of determining the integrity of the filters. The usual test, that of proving their ability to retain microörganisms of ordinary size, was obviously out of the question, as the *B. bronchisepticus* is one of the smallest of known organisms.

A test known for several years, and well described by Bulloch and Craw (1909[1]), was finally decided to be the most reliable. This test depends upon the measure of the pressure of air as it is allowed to pass through the pores of the filter while immersed in water. A leakage at any point or a variation in the texture or thickness of the walls can be detected at once, the efficiency of the filter measured to a fraction of a pound and the porosity of

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various filters compared merely by observing the pressure necessary to produce a general flow of air through the pores of the candles proper.

As an example of the value of this test, twelve each of Berkefeld N, Berkefeld V, and Pasteur F candles, taken directly from the original packages, were tested with the following results:

BERKEFELD V CANDLES.

Candles.	Leakage at Joint.	General Flow of Air through Candle.
1	1 lb. of air pressure per square inch.	6 lb. pressure.
2	1 " " "	5 " "
3	2 " " "	3 " "
4	1 " " "	5 " "
5	2 " " "	2 " "
6	1 " " "	6 " "
7	1 " " "	4 " "
8	1 " " "	6 " "
9	1 " " "	3 " "
10	4 " " "	4 " "
11	1 " " "	6 " "
12	2 " " "	3 " "
Average	1.5	4.3

BERKEFELD N CANDLES.

13	6 lb. of air pressure per square inch.	9 lb. pressure.
14	5 " " "	8 " "
15	1 " " "	9 " "
16	3 " " "	12 " "
17	5 " " "	14 " "
18	2 " " "	12 " "
19	2 " " "	11 " "
20	2 " " "	10 " "
21	1 " " "	10 " "
22	11 " " "	11 " "
23	7 " " "	14 " "
24	1 " " "	10 " "
Average	3.8	10.8

CHAMBERLAND F CANDLES.

25	23 lb. of air pressure per square inch.	29 lb. pressure.
26	19 " " "	22 " "
27	18 " " "	29 " "
28	19 " " "	19 " "
29	20 " " "	21 " "
30	16 " " "	21 " "
31	19 " " "	21 " "
32	19 " " "	21 " "
33	14 " " "	21 " "
34	15 " " "	21 " "
35	17 " " "	29 " "
36	15 " " "	23 " "
Average	17.8	23.9

It can readily be seen that, in estimating the efficiency of any candle, the leakage at the joint must be seriously considered. The average pressure of the flow of air through the candle of the Berkefeld V filter was 4.3 lb., while the leakage at the joint was, on the average, 1.5 lb. The average flow of air through the Berkefeld N candles was 10.8 lb., while the leakage at the joint averaged 3.8 lb., a difference of 7 lb. Even with the Pasteur candles there was a difference of 6.1 lb. between the flow of air at the joint and that of the candle proper. While the Berkefeld N filters, Nos. 15, 21, and 24, were very efficient, as far as the candles were concerned, recording pressures of 9, 10, and 10 lb. respectively, they were valueless as testers of filter passers, since they all leaked at the joints with a pressure of 1 lb. Candles Nos. 16, 18, 19, and 20 were also of no value, due to leakage at the joint, although the leakage did not take place until the gauge showed a pressure of 2 or 3 lb.

For the experiments recorded in this paper, seven of the above candles were chosen (the Berkefeld N candle, No. 22, and Pasteur F candles, Nos. 25, 26, 28, 29, 31, and 32). They showed no signs of leakage or weakness at any point and gave very high efficiency, as recorded by the pressure gauge.

In carrying on our experiments the organism in question was grown twenty-four hours, both on agar and in bouillon. The bouillon growth was filtered undiluted, while the agar growth was taken off in bouillon and made into a suspension of about the same density as the bouillon culture. The filtration was conducted at room temperature, one hour taken as the length of time for filtration, and three pressures were used—gravity, 15 lb. negative and 225 lb. positive.

The results of the work proved conclusively, according to all rules as laid down by the several authorities on filterable viruses, that the *B. bronchisepticus* is a filterable organism. The work also corroborated the results of previous investigators with regard to the fact that the less pressure used the more easily will some organisms pass through the filters.

Some very interesting possibilities are suggested by the outcome of this work. Since 1905, when Carré ([5]) claimed that he had produced typical symptoms of distemper in susceptible dogs, from the filtered discharges of diseased dogs, the majority of

writers have classified the etiology of canine distemper as a filterable, invisible, or ultramiscroscopic virus, and it is so described in many text-books. The results of the work of Ferry, McGowan, and Torrey with the *B. bronchisepticus* tended to refute the statements of Carré, especially as their work was carried on at the same time and quite independently, thus lending great weight to their claims. The work of Carré, however, is not entirely disregarded, many still accepting his position. The results of the filtration experiments with the *B. bronchisepticus* put an entirely new light on the subject. If the *B. bronchisepticus* is the cause of canine distemper, then the experiments corroborate the work of Carré. If the work of Carré was correct, and if the causative agent of canine distemper is a filterable virus, then the experiments point very conclusively to *B. bronchisepticus,* and confirm the findings of the three previously mentioned investigators.

Because of the variation in rules laid down by different authorities for the method of procedure to be used in attempting to prove the presence of a filterable virus, and from the many inconsistencies in the definitions offered for filterable or invisible viruses, the author has often been at a loss to know exactly what is meant by these terms. It is very certain that the term "filterable virus" is rapidly gaining in popularity over the terms "invisible or ultramicroscopic virus," and rightly so, and yet the terms are still used interchangeably by many authors in spite of the fact that filterability does not necessarily imply invisibility. In speaking of a filterable virus, many still think in terms of invisibility, shutting out of their minds entirely the hope of ever being able to consider the unknown virus as anything tangible or visible. In fact, in two well-known text-books on bacteriology, we find in one (1912[9]) a chapter on invisible viruses which defines an invisible organism in terms of filterability, and in the other (1914[6]) a chapter on filterable viruses in which a filterable virus is defined in terms of invisibility. Neither of these definitions can be correct, as a filterable virus need not necessarily be invisible, and an invisible virus can readily be conceived of as large enough to be retained by the ordinary filter. Jordan (1914[6]) says: "There have been many instances in the history of bacteriology when failure to render a microörganism visible has been finally found

to depend upon other factors than simple minuteness." Meyer (1914[7]), in a paper on filterable viruses, presented at the meeting of the Tenth International Veterinary Congress this year, says: "The conception of an 'invisible or ultramicroscopic virus' has been entirely abandoned since Bordet, Dujardin-Beaumetz, Borrel, v. Prowazek, Paschen, and others have explained that some of the filter passers at least can be demonstrated microscopically." It is very evident, however, that the conception of an invisible virus has not been entirely abandoned, for Panissett (1914[8]), at the same meeting, presented a paper entitled: "Les Virus Ultramicroscopiques." In corroboration of Meyer's statement, however, he says: "The idea of invisibility is relative and temporary. It may disappear with new methods of investigation. It is, therefore, preferable to adopt filterability as the criterion for the study of these viruses and describe them as filterable viruses."

In the light of the fact that so much work is being done at present on diseases of unknown origin, and those known to be due to filterable viruses, it is very evident that the term "invisible virus" will finally be discarded in favor of the term "filterable virus," which, in classification, will be used for some time to come. It is, therefore, essential that there should be some general uniform method to follow while attempting to demonstrate the presence of viruses in this class.

The science of bacteriology to-day is based on uniformity of methods. We have uniform methods for the preparation of culture media, uniform methods for testing and identifying microörganisms, uniform methods of water analysis, and an attempt at a uniform method of classification. Now that so much work is being done on diseases due to unknown organisms belonging to the class known as "filterable viruses," there ought to be some uniform method of demonstrating their presence, of testing the efficiency of the candles, and expressing or recording the results. It seems to be agreed by all authorities that some sort of a uniform plan of procedure should be followed, and we have, as a result, as many uniform methods as there are articles on the subject. One authority says the existence of an invisible microorganism is determined as follows: "The infectious agent must pass through a bacteria-proof filter, which is free from imperfections, as shown by tests with visible organisms of small size.

Pressure exceeding one atmosphere should not be employed during filtration. The time of filtration should not exceed one hour. The filtrate should remain free from all visible bacteria, as shown by microscopic examination and cultural tests. The filtrate should possess the specific disease-producing qualities of the unfiltered material. Animals infected with the filtrate should yield material which, after filtration, will in its turn possess the attributes of the original unfiltered material."

Another author says: "The filtration must be completed within as short a time as possible, always within two hours." He also says: "The pressure—positive or negative—used in filtration should not exceed 500 mm. of mercury." "In order to lessen the protein content of the fluid to be filtered, dilution with sterile water or salt solution, 1:40 to 1:100, is desirable." "The integrity of the filter and the freedom of the filtrate from ordinary bacteria should always be determined. Organisms, like *B. pyocyaneus*, are sometimes added as test-objects to the fluid to be filtered."

An English translation of a well-known French text-book (1913[10]) gives us the following: "To demonstrate this property —filterability—too fine a filter must not be used." It also adds: "The filter should be new and must be sterilized before use; the process of filtration should occupy not more than about two hours; the pressure applied, whether by compression or aspiration, should be as small as possible (in the former case, say, the pressure produced by an india-rubber syringe, and in the latter that equivalent to 50 to 500 mm. of mercury)."

The author realizes the difficulties, at present, of prescribing exact rules for determining the filterability of any known or unknown microörganism. He believes, however, that the time is ripe for the attempt, at least, of working out some uniform method of carrying on filtration experiments, and that this society is the logical body to formulate such a plan of procedure.

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76. Inoculation Experiment with Pure Culture of Spirochæta Hyos—Studies on Hog Cholera. By Walter E. King and Raymond H. Drake. (*Journal of Infectious Diseases,* Vol. 16, Jan., 1915, pp. 54-57.)

77. What is the Best End-Point of the Reaction in the Frog-Heart Method of Digitalis Assay? By H. C. Hamilton and L. W. Rowe. (*Journal of the American Pharmaceutical Association,* Vol. 4, January, 1915, pp. 108-112.)

78. The Glands of Internal Secretion and Their Importance as Therapeutic Agents. By Carey P. McCord. (*Journal of the American Pharmaceutical Association,* Vol. 4, March, 1915, pp. 293-297.)

79. Cannabis Sativa. By H. C. Hamilton. (*Journal of the American Pharmaceutical Association,* Vol. 4, April, 1915, pp. 448-451.)

80. The Pineal Gland. By Carey P. McCord. (*Interstate Medical Journal,* Vol. 22, No. 4, April, 1915, pp. 354-370.)

81. The Filterability of Bacillus Bronchisepticus: With An Argument for a Uniform Method of Filtration. By N. S. Ferry. (*Journal of Pathology and Bacteriology,* Vol. 19, No. 4, April, 1915, pp. 488-493.)

THE PINEAL GLAND IN RELATION TO SOMATIC, SEXUAL AND MENTAL DEVELOPMENT.

SECOND PAPER.

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Current descriptions of the pineal gland attribute to this organ the function of producing a secretion which inhibits growth of body and restrains mental and sexual development from exceeding the rate looked on as normal for preadult life. This inference arises from the occasional distinctive precocity of development following invasion of the pineal gland by neoplasms. It is assumed that such neoplasms destroy the gland, and that any resulting metabolic disturbances occur from the deprivation of the body of the pineal's elaborated substances.

From a reactionary point of view, the groundwork for such a theory is both meager and unstable. From sixty-five to seventy authentic cases of pineal tumors have come under observation. These have been distributed over more than a century. Copies of the original descriptions are rarely readily accessible. By reason of faulty translations and inaccuracies in quotations, some descriptions of pineal gland syndromes have come to resemble classical myths. Of the sixty-five to seventy cases, only about 10 per cent present those striking effects characterized as the "precocious macrogenitosomatic pineal syndrome." The instances of greatest metabolic disturbances have occurred in persons below 14 years of age. Of the total number of cases, sixteen were recognized before the age of 14 was attained—twelve boys and four girls. The syndrome has appeared in more striking form in boys than in girls, but the ironclad statement that the syndrome is confined to males is probably unwarranted. Marburg's case in a girl of 9 presents metabolic alterations equally as striking as those in boys cited as types of the pineal syndrome. It is noteworthy that the pineal syndrome has occurred only in such cases of pineal tumors as have led to an obstructive hydrocephalus and thus, of necessity, to secondary hypophysial disturbances (Cushing).

In the remainder of the total sixty-five to seventy pineal cases, there appear various departures from the established syndrome. The greater number, whether adults or children of either sex, manifest no metabolic disturbances attributable to pineal functional perversion. The nicety of the theory that only in childhood and only in boys does this syndrome appear, is apparently jeopardized by the occurrence of pineal tumors with adiposity in adults of both sexes, with adiposity and infantilism in both sexes, and with cachexia. In part, these deviations from anticipated findings are due to secondary involvement of others of the endocrinous system, notably the hypophysis. The interrelation with others of the glandular system has been emphasized by Marburg, Fränkl Hochwart and others, but in some instances the necropsy demonstration of a pineal tumor led to the crediting of all prior changes to pineal dysfunction.

The available histories frequently do not permit a restudying in the light of later developments in our knowledge of the interrelation of the several glands. When this is possible, many of the apparent discrepancies and conflicts are rendered more nearly harmonious through evidence of involvement of other glands, especially the hypophysis, and secondary to it the sex organs. When, however, a delineation is made of the extent of these secondary influences and these are hypothetically set apart, there still remain alterations probably attributable only to primary pineal dysfunction. The complete syndrome is characterized by (1) overdevelopment of the sex organs, both anatomic and functional; (2) precocity of mental development; (3) general overgrowth of body with or without adiposity—the whole picture being one of early maturity. The syndrome is rarely complete. The most nearly complete cases have occurred in boys below or near 7 years of age. It is at this age rather than at puberty that the gland presents its greatest histologic evidence of a beginning involution.

A second pineal syndrome whose essential feature is cachexia has been described. This is much less definitely connected with pineal dysfunction, and has been more especially associated with the occurrence of tumors in adult life. It is described as representing apincalism.

The nature of the pineal syndrome, whether it be the out-

growth of hyperpinealism or hypopinealism, or whether a clinical condition corresponds to each of these deviations from normal, is not established. On the recognition of a specific pineal syndrome (or syndromes), efforts were made to establish its cause by reproducing the condition in animals through the experimental removal of the gland. The gland's extirpation is difficult, but has been successfully performed in both young and adult animals. The results are rendered less authoritative by the vitiating effects of the trauma necessary in the gland's removal. Pinealectomy determined no changes that might be associated with pineal functions as observed by the majority of investigators. Foa and Sarteschi, respectively, report that, of the animals which survived the operative procedures, some young males evinced certain features of the pineal syndromes. The similarity on comparison with clinical cases is remote.

The precocious macrogenitosomatic syndrome is usually ascribed to hypopinealism. The theory suggested above as current assumes that pineal lesions are destructive, and that concomitant metabolic disturbances arise from the lack of pineal secretion. To the contrary, running through the publication of a number of observers are to be noted suggestions that pineal neoplasms retain some of the functional characteristics of normal pineal cells, and that the pineal syndrome is due to increased rather than decreased function of the gland. The similarity of pineal tumor cells to normal pineal cells has been pointed out by Howell.[1] The retention of function in neoplasms in other glands is not infrequent; tumors in the hypophysis have in a number of cases occasioned acromegaly, a hyperpituitarism; tumors of the thyroid and metastases from thyroid tumors may secrete typical thyroid colloid; suprarenal gland neoplasms yield the active principle of the normal suprarenal; bile is secreted by certain liver tumors, whether they be located in the liver or metastasized to other portions of the body. The inference from such instances is that the cells of the neoplasm originating in an organ may, under certain conditions, retain some of the functional attributes of the normal cells of that organ. That pineal tumors may lead to an active constructive stimulating influence (hyperpinealism)

1. Howell, Hinds: Proc. Roy. Soc. Med. (Neurolog. Sec.), 1910, iii, 65.

is suggested in publications by Marburg,[2] Polavani,[3] Oestreich and Slawyk[4] and Askanazy.[5] However, the evidence used by Marburg may readily be turned to support the idea of hypophysial involvement in his case. Oestreich and Slawyk regard the early sexual maturity as hyperpinealism analogous to acromegaly from hyperpituitarism. Askanazy suggests that teratomas may be regarded as "false conceptions," in which one might expect, primarily at least, an increase in the pineal secreting functions (compare Bailey and Jelliffe). It is noteworthy that the best-defined cases of pineal syndromes regularly occur from pathologic conditions invading the actual tissue of the gland, rather than from simple cysts and from adjacent tumors involving the pineal only by compression.

In this rather uncertain situation, it is held that, in case uniform and consistent manifestations followed the experimental administration of pineal gland tissue, and these manifestations stood in some qualitative relation to evidence as to function derived from other sources, such experiments, rigidly controlled, would be acceptable as bearing on the functions of the gland. Accordingly, such experiments have been performed. The results have been indicated in part in a preliminary report.[6] A report of results from a continuation of this earlier work constitutes the remainder of this paper.

EXPERIMENTAL DATA.

Feeding experiments with small animals, in which the results are measured in such terms as weight differences and body disproportions, are so vitiated by trivial differences in the living conditions of the experimental and control animals that any deductions should be made most guardedly. The findings from a single series of feeding experiments might easily be misinterpreted because of some deleterious influence of obscure origin. When, however, the investigation includes a number of series of animals, and the different series are maintained under varied experimental conditions, no accidental influence would constantly

2. Marburg: Wien. med. Wchnschr., 1908, lviii, 2617.
3. Polavani: Lab. Note-Biologica, 1913, vii, 655.
4. Oestreich and Slawyk: Virchows Arch. f. path. Anat., 1899, clvii, 155.
5. Askanazy: Verhandl. d. deutsch. path. Gesellsch., 1906, p. 58.
6. McCord, C. P.: The Pineal Gland in Relation to Somatic, Sexual and Mental Development, *The Journal A. M. A.*, July 18, 1914, p. 232.

be exerted on a single phase of the experimentation. Any deviations from the normal, regularly appearing in the several experimental groups, may be attributed to the influence of the substances employed in feeding.

Because of this facility with which abstruse errors enter into feeding experiments, the preliminary work, which included results from feeding chicks, guinea-pigs and puppies, has been extended to include results from 393 animals. Variations have been introduced, in dosage, in methods of administration, in source of material used (species and age of animals supplying glandular material) and in age of test animals. Except for one series of experiments on the influence of the pineal on embryonic development, guinea-pigs have been exclusively employed as test animals.

THE INFLUENCE OF PINEAL GLAND ADMINISTRATION AS SEEN IN WEIGHT DIFFERENCES.

(*a*) *Effect of feeding the pineal substance from old adult cattle to young animals.*

Series A (forty-eight young pigs, aged 2 weeks, an equal number of males and females, sexes maintained apart) was equally divided into control and experimental lots. To the experimental lot, 10 mg. of pineal tissue from adult cattle was daily administered by mouth. The controls were similarly given a corresponding amount of inert material. This was continued ten weeks with weekly weighings. Since to the pineal are attributed functions confined to preadult life, it might be anticipated that feeding with mature glandular material would cause no change. On the other hand, the histologic picture of the adult pineal indicates the persistence of some glandular elements throughout life. The two lots of animals under observation as to this point ran essentially parallel weights. At the end of the ten weeks, the experimental animals had gained on an average of 130.5 per cent., while the controls gained 136.5 per cent.

As a check on Series A, Series G was similarly carried out with results as indicated in Table 1.

(*b*) *The effect of administering veal pineal glands to old experimental animals.*

The counterpart of the foregoing experiments was also undertaken. All earlier experiments in which the work was begun with young animals, but continued to the time of adult life, contribute data to this present phase of inquiry. Whenever it has been possible to induce a rapid body growth in immature animals, it has never been possible to continue this excessive growth above normal adult size. As the animals approach adult size, the pineal feeding is less effective, and after full maturity is reached, is without effect. There has, at no time, been a tendency toward gigantism.

Male guinea-pigs are sexually active before 4 months, and at 6 months are considered mature adults. However, these bucks subsequently slowly increase in size for several months before attaining their maximum weight. Series F (all males) was directed toward this period of growth. The animals were picked at 6 months of age, fed veal pineal tissue, and controlled as in other reported series. The feeding was maintained for four weeks, but weighings were continued for eight weeks. In this period the average experimental buck gained 167.6 gm., while the average control gained 121.4 gm.

TABLE 1.—RESULTS OF FEEDING ADULT PINEAL GLAND TO YOUNG MALE GUINEA-PIGS· (Series G)

Control, 12 Pigs Average Initial Weight, 197.6 gm. Age, 2 weeks			Pineal, 12 Pigs Average Initial Weight, 199.8 gm. Age, 2 weeks		
Weeks	Aver. Wt., Gm.	Gain, Gm.	Weeks	Aver. Wt., Gm.	Gain, Gm.
1	233.4	35.8	1	228.1	28.3
2	264.4	31.0	2	255.1	27.0
3	294.7	30.3	3	277.0	21.9
4	323.0	28.3	4	307.1	30.1
5*	349.1	26.1	5*	334.3	27.2
6	385.2	36.1	6	365.5	31.2
7	431.6	46.4	7	403.6	38.1
8	444.0	12.4	8	425.3	21.7
Average weight at end of eighth week..... 444.0 gm. Average initial weight.... 197.6 gm.			Average weight at end of eighth week..... 425.3 gm. Average initial weight.... 199.8 gm.		
Average gain..... 246.4 gm. Gain per cent. 124.7			Average gain..... 225.5 gm. Gain, per cent. 112.7		

* Feeding discontinued.

(c) The effect of administering pineal glands from young animals to young experimental animals.

The greater portion of the data of the original paper is directed toward this phase. Of the more recent work, Series C, D, E and E_2 (hereinafter described, Table 3) contribute data.

Hypodermic Injections of Pineal Extracts: Several glandular principles are not sufficiently stable to survive the deleterious action of the digestive juices and the liver, and thus are not efficacious when administered orally. Whatever principles there may be in the pineal gland seem to pass through the digestive processes sufficiently intact to induce metabolic changes. To determine the comparative effects of pineal extracts administered orally and hypodermically, Series D (forty-eight young pigs, both sexes) was aseptically injected triweekly with 20 mg. of veal pineal tissue in 1 c.c. of water. The controls were injected with an equal quantity of brain tissue similarly prepared. A comparison of results from D with

those obtained from the oral administration to animals of the same age is shown in Table 2.

In Series E and E_2, another variation was introduced by the substitution of lamb pineal tissue for that of veal and cattle. The gland in lambs is of different shape from that found in cattle. The lamb gland is round instead of oval, the melano pigment is (when present) localized in the distal organ. The lamb glands weigh, on an average, 100 mg. The method of preparation of this tissue was the same as that earlier described. Such material was administered to the animals of Series E in 10 mg. amounts daily. The results are indicated in the general tabular summary. To E_2, 100 mg. of the same tissue was administered. This larger dose was evidently not well borne by the alimentary tract, for, during the eleven weeks of feeding, there were irregular periods of distinct loss of weight. Ultimately, however, an excess of 40.9 per cent. was determined as the gain of pineal fed over control animals.

TABTE 2.—COMPARISON OF RESULTS OBTAINED FROM ORAL ADMINISTRATION OF VEAL PINEAL GLAND WITH THOSE FROM HYPODERMIC ADMINISTRATION

Oral				Hypodermic			
Weeks	Gain Per Cent., Control	Gain Per Cent., Pineal	Per Cent. Difference	Weeks	Gain Per Cent., Control	Gain Per Cent., Pineal	Per Cent. Difference
2	9.3	10.9	1.6	2	17.2	36	18.8
4	24.7	32.5	7.8	4	30.4	45	14.6
6	32.	49.3	17.3	6	36.2	56	19.8

(*d*) *Difference in effect of pineal administration on animals of different sex.*

The pineal clinical syndrome has been best established in males. In extirpation experiments, only in males have metabolic disturbances been described. Because of this apparent predilection for males, the results of feeding have been analyzed for data as to the relative responsiveness of the two sexes. Series E and a part of B have been analyzed. Early it was obvious that both males and females responded to pineal stimulation. It was anticipated that the males would make greater gains than females in both the control and experimental lots. Computations have been based on gains of experimental males over control males in comparison with gains of experimental females over control females. On such a basis, two-thirds of the excess gains are made by male animals. This was observed in Series E, in which the total period determined a general excess of 19.3 per cent. in favor of experimental animals. Analysis of this gain by sex indicates a 25.8 per cent. gain for the males, and for the females, 12.7 per cent. Details of the analysis of Series B are given in Table 4.

(*c*) *Summary and comment on weight differences.*

The data accruing from two years of feeding experiments with pineal substance are sufficiently extensive to free the results of accidental vitiating factors. Averages of a number of experimental series aggregating nearly 400 animals would indicate that young animals to which had been administered pineal tissue developed at a rate in excess of normal controls.

The most pronounced results arose from the feeding of young animals with material derived from young animals.

TABLE 3.—PERCENTAL GAINS OF VARIOUS SERIES DURING SIX WEEKS' GROWTH

Series	Second Week		Fourth Week		Sixth Week	
	Control	Pineal	Control	Pineal	Control	Pineal
B	9.3	10.9	24.7	32.5	32.0	49.3
C	26.3	26.6	45.3	47.6	71.5	83.1
D	17.2	36.0	30.4	45.9	36.2	56.0
E	21.2	24.6	45.9	50.6	59.3	78.4
E_2	27.7	22.6	47.0	53.3	68.7	82.4

Although some histologic evidence exists indicating the glandular nature of the pineal in mature adult life, such material, when fed to young animals, did not bring about the changes observed in feeding with younger pineal material.

At no time has gigantism been produced. As adult life is approached, pineal feeding is less effective.

The excess growth of young animals under pineal feeding is grossly symmetrical. No disproportion has been observed except a possible hypertrophy of the tests noted in some animals. In microscopic sections, such testes are seen to be made up of larger and more mature tubules than in controls of the same age, but with no increase in the interstitial tissue.

Both males and females are affected by pineal administration, but the gains (in relation to respective controls) have been greater for the males than for females.

THE INFLUENCE OF PINEAL FEEDING ON SEXUAL MATURITY.

Of any several groups of premature guinea-pigs maintained under normal conditions, it is assumed that individuals will attain to sexual maturity near the same time and will give birth to young at about the same subsequent time. In case of a regularly recurring marked difference in time of birth of first young in one phase of an experimental lot of animals, it is rational to associate this phenomenon with different times of attaining to maturity. On such a basis it has been noted in all groups of animals which were allowed to breed that the pineal-fed mothers gave birth to young earlier than the controls. One series including forty-five animals was carefully conducted with a view to any data bearing on the matter in

question. The two sexes were kept together from birth. The feeding with veal pineal tissue was continued for fourteen weeks. During this time the pineal-fed attained to a size 32 per cent. larger than their controls of the same ages. The female farthest advanced in pregnancy among the pineal-fed animals aborted, so that the date of birth of first young was not determined. The first normal birth occurred July 3 in the experimental group. Others of the same group followed until over half the females had given birth to young. Then three weeks and two days later, July 26, the first control pig was born. The progeny in all instances were like any other pigs. After all pigs were born in both groups and after an interval of several weeks, the same females were placed with normal bucks to detect a possible difference in the second pregnancy. No such difference was detectable.

TABLE 4.—ANALYSIS OF GAINS BY SEX (Series B)

Weeks	Control, 2 Weeks Old				Pineal, 2 Weeks Old			
	Males		Females		Males		Females	
	Aver., Gm.	Gain, Gm.	Aver., Gm.	Gain, Gm.	Aver., Gm.	Gain, Gm.	Aver., Gm.	Gain, Gm.
	200.9	....	205.9	....	204.5	....	208.4	....
1	200.0	—0.9	192.0	—13.9	203.2	—1.3	211.9	3.5
2	219.9	19.9	219.8	27.8	249.0	45.8	224.9	13.0
3	251.5	31.6	224.4	4.6	284.1	35.1	242.3	17.4
4	277.7	26.2	250.1	25.7	309.9	25.8	259.1	16.8
5	295.5	17.8	266.2	16.1	331.8	21.9	277.4	18.3
6	296.7	1.2	262.7	—3.5	342.1	10.3	282.8	5.4
7	326.2	29.5	288.6	25.9	373.3	31.2	305.2	22.4
8	345.3	19.1	305.5	16.9	401.5	28.2	325.2	20.0
9	360.9	15.6	314.0	8.5	409.8	8.3	326.1	0.9
10	402.2	41.3	349.4	35.4	452.2	42.4	371.4	45.3
11	417.5	15.3	367.8	18.4	479.0	26.8	387.4	16.0
12	427.4	9.9	379.7	11.9	482.8	3.8	402.5	15.1
13	433.3	5.9	383.4	3.7	488.5	5.7	421.6	19.1
14	458.1	24.8	413.9	30.5	522.4	33.9	444.3	22.7

	Males	Females	Males	Females
Last weight....	458.1 gm.	417.9 gm.	522.4 gm.	444.3 gm.
Initial weight..	200.9 gm.	205.9 gm.	204.5 gm.	208.4 gm.
Average gain...	257.2 gm.	212.0 gm.	317.9 gm.	235.9 gm.
Gain per cent...	128.0	103.0	155.4	113.2

Excess pineal males over control males..... 27.4 per cent.
Excess pineal females over control females..... 10.2 per cent.

GENERAL SUMMARY.

From the foregoing experiments, evidence of the precocity of development usually attributed to pineal deficiency (hypopinealism) has been obtained in animals by supplying an increased amount of pineal substance by feeding or injecting pineal prepa-

rations. Such administration of pineal substances led to a more rapid growth of body than normal, and determined an early sexual maturity. The excess in rate of growth was most pronounced (40.9 per cent. excess in eleven weeks) in *young* animals fed with pineal tissue obtained from *young* animals. No tendency to gigantism has followed pineal administration. After maximum size was attained, pineal administration appeared to be ineffective. Both males and females respond to the influence of pineal substances in rate of growth, but the response has been more definitely manifested in males.

REPRINTS OF PUBLICATIONS FROM THE RESEARCH LABORATORY, PARKE, DAVIS & CO., DETROIT, MICH.

The present system of collecting reprints of articles published from the Research Laboratory was begun in 1912. Reprints of the following articles published subsequent to that time are available and will be sent upon request. The publications marked (*) are no longer available.

1. On the Administration of Diphtheria Toxin in a Collodion Sac. By E. C. L. Miller. (*Journal of Infectious Diseases,* Vol. 8, January, 1911, pp. 50-65.)

2. A Further Contribution to Our Knowledge of Insecticides—Fumigants. By Chas. T. McClintock, H. C. Hamilton and F. B. Lowe. (*Journal of the American Public Health Association,* Vol. 1, April, 1911, pp. 227-238.)

3. Duboisia Hopwoodii—A Histological Study. By Oliver A. Farwell. (Reprinted from *Merck's Report,* Vol. 20, May 1, 1911.)

*4. Etiology of Canine Distemper. By Newell S. Ferry. (*Journal of Infectious Diseases,* Vol. 8, June, 1911, pp. 399-420.)

*5. The Resistance of Smallpox Vaccine to the Coal-tar Disinfectants. By Chas. T. McClintock and Newell S. Ferry. (*Journal of the American Public Health Association,* Vol. 1, June, 1911, pp. 418-419.)

6. Production of Immunity with Over-Neutralized Diphtheria Toxin. By Chas. T. McClintock and Newell S. Ferry. (*Abdruck Aus Dem Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten,* Abt. 1, Originale, Bd. 59, July 15, 1911, pp. 456-464.)

7. Soaps from Different Glycerides—Their Germicidal and Insecticidal Values Alone and Associated with Active Agents. By H. C. Hamilton. (*Journal of Industrial and Engineering Chemistry,* Vol. 3, August, 1911, pp. 582-584.)

*8. The Sleepy Grass of New Mexico: A Histological Study. By Oliver A. Farwell. (*Merck's Report,* Vol. 20, October, 1911, pp. 271-273.)

*9. Some Observations on the Physiological Action of Sleepy Grass. By A. W. Lescohier. (*Merck's Report,* Vol. 20, October, 1911, pp. 271-275.)

*10. An Investigation of the Depressor Action of Pituitary Extracts. By Carey P. McCord. (*Archives of Internal Medicine,* Vol. 8, November, 1911, pp. 609-620.)

11. The Physiology of the Pituitary Gland and the Actions of Its Extracts. By Carl J. Wiggers. (*American Journal of Medical Sciences,* Vol. 141, April, 1911, pp. 502-515.)

12. A Physiological Investigation of the Treatment of Hemoptysis. By Carl J. Wiggers. (*Archives of Internal Medicine,* Vol. 8, 1911, pp. 17-38.)

13. Notes on Catgut Sterilization: A Preliminary Report. By Willard H. Hutchings. (*Annals of Surgery,* Vol. 54, July, 1911, pp. 693-695.)

14. The Relations of Pyogenic Microorganisms to the Etiology and Treatment of Skin Diseases. By Henry Rockwell Varney. (*Ohio State Medical Journal,* December, 1911.)

15. A Micrococcus with Unusual Characteristics as a Factor in a Resistant Dermatosis Resembling Acne Vulgaris. By Henry Rockwell Varney and L. T. Clark. (*Journal of Cutaneous Diseases,* Vol. 30, February, 1912, pp. 72-78.)

16. Serum Treatment of Hemorrhage and Blood Dyscrasias. By A. W. Lescohier. (*New York Medical Journal,* Vol. 95, February 3, 1912, pp. 223-229.)

*17. Further Studies on the Bacillus Bronchicanis, the Cause of Canine Distemper. By Newell S. Ferry. (*American Veterinary Review,* Vol. 41, April, 1912, pp. 77-79.)

18. The Pharmacopœial Requirements for Cannabis Sativa. By H. C. Hamilton. (*Journal of the American Pharmaceutical Association,* Vol. 1, March, 1912, pp. 200-203.)

19. The Heart Tonic Unit. By H. C. Hamilton. (*American Journal of Pharmacy,* Vol. 84, March, 1912, pp. 97-103.)

20. Studies on the Etiology of Equine Influenza. By Newell S. Ferry. (*Veterinary Journal* (London), Vol. 19, April, 1912, pp. 185-197.)

21. A Method for the Bacteriological Standardization of Disinfectants. By Tatsuzo Ohno and H. C. Hamilton. (*American Journal of Public Health,* Vol. 2, May, 1912, pp. 331-338.)

22. Physiological Testing. By E. M. Houghton. (*American Druggist,* July and September, 1911, and January and April, 1912.)

23. Bacillus Bronchisepticus (Bronchicanis): The Cause of Distemper in Dogs and a Similar Disease in Other Animals. By Newell S. Ferry. (*Veterinary Journal* (London), Vol. 19, July, 1912, pp. 376-391.)

24. On Feeding Young Pups the Anterior Lobe of the Pituitary Gland. By T. B. Aldrich. (*American Journal of Physiology,* Vol. 30, July, 1912, pp. 352-357.)

25. A Practical Portable Incubator. By Newell S. Ferry. (*Abdruck Aus Dem Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten,* Abt. 1, Original, Bd. 65, Heft 4/5, 1912, pp. 412-413.)

26. Tobacco Extracts: Their Comparative Values as Insecticides. By W. O. Hollister. (*Journal of Economic Entomology,* Vol 5, June, 1912, pp. 263-267.)

27. The Pharmacological Assay of Pituitary Preparations. By H. C. Hamilton. (*Journal of the American Pharmaceutical Association,* Vol. 1, October, 1912, pp. 1117-1119.)

28. Pituitary Extracts in Obstetrics and Gynecology. By A. W. Lescohier and O. E. Closson. (*Journal of the Michigan State Medical Society,* Vol. 11, October, 1912, pp. 650-657.)

29. Biological Products—Veterinary. By Robert H. Wilson. (*American Veterinary Review,* Vol. 41, September, 1912, pp. 668-681.)

30. The Isolation and Cultural Characteristics of Bacillus Acne. By Edwin M. Stanton. (*Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten,* Original, Bd. 66, Heft 5/7, 1912, pp. 386-389.)

31. Studies on Hog Cholera. By Walter E. King and Robert H. Wilson. (*Journal of Infectious Diseases,* Vol. 11, Nov., 1912, pp. 441-458.)

32. Studies on the Virus of Hog Cholera. By Walter E. King and F. W. Baeslack. (*Journal of Infectious Diseases,* Vol. 12, Jan., 1913, pp. 39-41.)

33. The Physiological Activity of Cannabis Sativa. By H. C. Hamilton, A. W. Lescohier and R. A. Perkins. (*Journal of the American Pharmaceutical Association,* Vol. 2, Jan., 1913, pp. 22-30.

34. The Iodine Content of the Small, Medium and Large Thyroid Glands of Sheep, Beef and Hogs. By T. B. Aldrich. (Original Communications, Eighth International Congress of Applied Chemistry, Vol. 19, 1912, pp. 9-14.)

35. Studies on the Virus of Hog Cholera. By Walter E. King and Robert H. Wilson. (*Zeitschrift für Immunitatsforschung und Experimentelle Therapie,* Bd. 16, Heft 3, 1913, pp. 367-376.)

36. On the Cultivation of the Treponema Pallidum (Spirochæta Pallida). By F. W. Baeslack. (*Journal of Infectious Diseases,* Vol. 12, Jan., 1913, pp. 55-67.)

*37. Studies on the Gonococcus, I. By Carl C. Warden. (*Journal of Infectious Diseases,* Vol. 12, Jan., 1913, pp. 93-105.)

38. Studies on the Virus of Hog Cholera. By Walter E. King, F. W. Baeslack and George L. Hoffmann. (*Journal of Infectious Diseases,* Vol. 12, March, 1913, pp. 206-235.)

39. Bacillus Bronchisepticus—Its Relation to Canine Distemper. By N. S. Ferry. (*American Veterinary Review,* Vol. 43, April, 1913, pp. 16-30.)

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67. The Sero-enzyme Test for Syphilis. By F. W. Baeslack, M.D., M.A. (*Journal of the American Medical Association,* Vol. 63, Aug. 15, 1914, pp. 559-563.)

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77. What is the Best End-Point of the Reaction in the Frog-Heart Method of Digitalis Assay? By H. C. Hamilton and L. W. Rowe. (*Journal of the American Pharmaceutical Association,* Vol. 4, January, 1915, pp. 108-112.)

78. The Glands of Internal Secretion and Their Importance as Therapeutic Agents. By Carey P. McCord. (*Journal of the American Pharmaceutical Association,* Vol. 4, March, 1915, pp. 293-297.)

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80. The Pineal Gland. By Carey P. McCord. (*Interstate Medical Journal,* Vol. 22, No. 4, April, 1915, pp. 354-370.)

81. The Filterability of Bacillus Bronchisepticus: With An Argument for a Uniform Method of Filtration. By N. S. Ferry. (*Journal of Pathology and Bacteriology,* Vol. 19, No. 4, April, 1915, pp. 488-493.)

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THE CORRECT NAME FOR THE HEMLOCK SPRUCE.*

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A casual perusal of the local floras covering eastern North America shows that the white spruce passes under the name of *Picea canadensis* (Mill.) BSP. and the hemlock spruce, of *Tsuga canadensis* (L.) Carr. Now, although Britton, Stearns, and Poggenberg quote Miller as the original author of the specific name *canadensis* of the white spruce, it becomes very evident through a perusal of Miller's description that his specific name is derived from the Linnaean *Pinus canadensis* and, therefore, that the proper citation (under article 41 of the Vienna rules) should include the name of Linnaeus, in parentheses, as the original author, instead of that of Miller. Here is, then, the anomalous position of two distinct species bearing the same specific name and both being derived from the same author, publication, and description, a condition contrary to all laws of botanical nomenclature, which provide that the specific name can be maintained for only one element of an aggregate when that aggregate is segregated. It remains, therefore, to determine which one of these two species shall retain the specific name *canadensis*. The first step is to determine if possible, what the Linnaean type of *Pinus canadensis* may be; if that can be determined, the rest willl be easy, for the type element of an aggregate will retain the specific name upon segregation.

The description of *Pinus canadensis* in the 2d edition of the Species Plantarum, 1763, on page 1421, is as follows:

10. PINUS foliis solitariis linearibus obtusiusculis *canadensis* submembranaceis.
    Abies foliis solitariis confertis obtusis membranaceis. *Gron. virg.* 191.*
    Abies foliis piceae brevioribus, conis parvis biuncialibus laxis. *Mill. dict. t.* I.
    Habitat in America *septentrionali.*

*Contributions to the Botany of Michigan, No. 10. Read at the St. Louis meeting of the Botanists of the Central States, October 17, 1914.

As there is no specific mention of a type we may arrive at one by considering (1) the herbarium specimens, (2) the description, (3) the synonyms, and (4) the specific name and habitat. *Pinus canadensis* is represented in the Linnaean Herbarium, but Mr. B. D. Jackson, in his Index to the Linnaean Herbarium, shows that the specimen was not received until later than 1767, several years after the publication of the species, and that it is not authenticated by Linnaeus; it may therefore be disregarded as not bearing upon the point in question.

The descriptive phrase of Linnaeus is not distinctive and can not limit his species to any one form; he took no consideration of the cones whatever; he described the leaves as solitary, linear, somewhat obtuse, and submembranaceous, characters that apply to the leaves of a number of species of the solitary-leaved Abieteae and therefore can not be considered as specific in character. The first synonym cited is that of Gronovius. Gronovius' species was published as follows on page 191 of the 1st edition of the Flora Virginica, part 2, 1743:

Abies *foliis solitariis confertis obtusus membranaceis.*

Abies minor pectinatis foliis Virginiana conis parvis, subrotundis. *Plukn. Alm. p.* 2 *t.* 121 *Fig.* 1

Abies minor Taxifoliis, conis parvis subrotundis, deorusm spectantibus. *Clayton N.* 517

Folia linearis, plana, tenuissima, carinata, obtusa, confertim natam solitaria. Coni magnitudine fragae, ovati, acuminati, squamis numerosis planis subrotundis obtusissimis.

In this connection it may properly be remarked that the plant of Plukenet, which is presumably the type of his figure 1, plate 121, is preserved in the Herb. Sloane, volume 95, folio 1, and is the hemlock spruce, generally known as *Tsuga canadensis* Carr.; also that the plant of Clayton, No. 517, upon which Gronovius based his species, is preserved at the British Museum and is the same thing.

Here we have not only a very accurate description of the leaves and cones but herbarium specimens and a published figure to supplement the descriptions, all of which, taken together, accurately limit the species defined to the hemlock spruce commonly known as *Tsuga canadensis* Carr. Apparently this should be definite enough to fix the status of *Pinus canadensis* L. But let

us go a little deeper into the question before taking up the next synonym. *If we take the first synonym enumerated under a species as the type of that species, in case no type is specifically named,* then *Pinus canadensis* L. becomes a pure synonym of *Pinus balsamea* L., for the first synonym cited under both species is the same Gronovian species, which is the hemlock spruce! Let us, thereforre, investigate the *Pinus balsamea* of Linnaeus, published on page 1002 of the 1st edition of the Species Plantarum in 1753, as follows:

Balsamea. 9. PINUS foliis solitariis submarginatis: subtus duplici punctata.

Abies foliis solitariis confertis obtusis membranaceis. *Gron. virg.* 191.*

Abies minor, pectinatis foliis, virginianna, conis parvis subrotundis. *Pluk. alm.* 2 *t.* 121. *f.* 1. *Raj. dendr.* 8.

Habitat in Virginia, Canada.

Habitus antecedentis [*Pinus Picea*], *sed* Folia *latiora, obtusiora, utrinque per ramos pectinatim digesta, at duplici serie, superiore sc. breviore, subtus sunt picta linea duplici glauca: singula ex 8 ordinibus longitudinalibus punctorum alborum.* Apex *foliorum saepe bifidus.*

A careful inspection of the above shows that it is an aggregate and composed of such divergent species as the balsam firs with *erect* cones and the hemlock spruce with *hanging cones.* To which element, then, under the rules of botanical nomenclature, does the name *Pinus balsamea* L. belong? There is unfortunately no rule covering this point in the Vienna rules nor, so far as the writer is aware, in any other code. There are no generic descriptions in the Species Plantarum and where there are specific diagnoses, these, from the modern point of view, are drawn so loosely in many cases that they are of little diagnostic value. Furthermore, the Species Plantarum is not considered to be a descriptive work but a mere application of the binomial system to the then known species—those that already had been published under the polynomial system by various older authors—and the species therein enumerated are considered to be based upon citations rather than upon the descriptive phrases. Should then the most

emphasis be placed upon the description or upon the citations? This is an important principle upon which no agreement has been reached; it ought to be definitely settled by a botanical congress, since very often, as in the present instance, widely different results may be obtained by different authors following out the different methods of treatment. Some authors prefer to adopt the descriptive matter as their guide, others the synonyms cited; so that we have such expressions as *Sonchus alpinus* L., as to character; or, as to the synonymy; or, as to the habitat, as the case may be. In the present instance, and it might be said in all instances of the kind, the best way is to let the internal evidence decide, adopting the name for that element which receives the preponderant weight of evidence. *If citations are considered to carry the greatest weight,* for the Species Plantarum is *par excellence* the work in which the binomial system is applied to citations, *then the name Pinus balsamea* L. *belongs to the hemlock spruce, for all the citations under that name are of this species.* The Linnaean herbarium contains no specimen which can be designated as the type, since it contained no specimen of the species at the time of its publication. Let us now look at the descriptive matter—the diagnostic phrase and the note under *Habitus.* There is absolutely nothing in the descriptive matter that will limit it to any one species; the cones are not at all considered; the characters ascribed to the leaves are applicable to other species than the balsam fir; in other words they are of a group or groupes of a higher order than that of a species, i.e., an aggregate. The same may be said of the habitat given, which is Virginia and Canada; the specific name is *balsamea,* and this alone is indicative of what Linnaeus may have had in view as the type of his species. As a matter of fact, the *Pinus balsamea* of Linnaeus is so broadly drawn that it may be appropriately considered a huge pit into which *all* the *spruces* and *firs* of eastern North America may be conveniently dropped to form a conglomerate whole. Notwithstanding the fact that the Species Plantarum is primarily a publication founded upon the woork of earlier botanists and that the binomials therein are mostly based upon and applied to the citations enumerated from those earlier botanists, we may be justified, in the present instance, in following precedent and in disregarding the synonyms cited and the description also, allowing the name

to represent the balsam fir; for this is undoubtedly the interpretation Linnaeus intended it to have as is indicated by the specific name.

Having excluded the hemlock synonyms from consideration under *Pinus balsamea* and having settled the status of that species we may resume consideration of *Pinus canadensis*. We have already shown that the first citation refers definitely to the hemlock spruce. We will now consider the Millerian synonym and endeavor to determine its status. This carries us back to the 7th edition of the "Gardeners Dictionary" published in 1759 and the "Figures" published in 1760. In the former work, Philip Miller has segregated the Linnaean aggregate and described four species from America under *Abies* as follows:

3. Abies *minor, pectinatis foliis, Virginiana, conis parvis subrotundis. Pluk. Alm.* The *Virginian* Fir Tree, with small roundish Cones, *commonly called* Hemlock Fir.
4. Abies *piceae foliis brevibus, conis minimus. Rand.* The Pitch-leaved Fir Tree, with small Cones, *commonly called* The *Newfounland* Black Spruce Fir.
5. Abies *piceae foliis brevioribus, conis parvis biuncialibus laxis. Rand.* The shortest Pitch-leaved Fir Tree with loose Cones, *commonly called* The *Newfoundland* White Spruce Fir.
6. Abies *taxi foliis, odora, Balsami Gileadensis, Raii Hist. App.* The Balm of *Gilead* Fir.

Here we have, so far as the writer is aware, the first post-Linnaean description of the species as they are understood at the present time. Unfortunately, Miller had not at that time accepted the binomial nomenclature of Linnaeus and consequently his species received no specific appellations; his work, however, can not be ignored any more than can the Species Plantarum itself. The descriptions and the notes on the following pages as to the native habitats, habits, etc., and the culture of the various plants in England leave no doubt whatever as to the identity of the species. No. 5 was illustrated in the following year, 1760, in the "Figures," and this is the species cited by Linnaeus under his *Pinus canadensis*. I have not seen the plate published by Miller but, considering the fact that he had a very clear conception of the various species and access to living material of all, I doubt not

but that it is characteristic of the white spruce.* We have no choice but to consider the 7th edition of the Gardeners Dictionary to be the publication in which the delimitation or segregation of our spruces and firs began and to be guided accordingly. It has become very clear from the foregoing that the *Pinus canadensis* of Linnaeus is an aggregate consisting of the hemlock spruce and the white spruce. The habitat gives us no clue as to which may be considered the type but the specific name, as in the case of *Pinus balsamea,* may. The white spruce is most characteristically a Canadian species, while the hemlock spruce is characteristically American, using the latter term as equivalent to the United States; hence the specific name indicates the white spruce. Also what more likely than that Linnaeus in establishing his *Pinus canadensis* was guided more by the *recently published but specifically unnamed* plate of Miller, than by the old description of Gronovius? We must also consider the fact that the *Plukenetian species, also illustrated and the true hemlock spruce, was left under Pinus balsamea.* The very fact that the hemlock spruce was divided between the two species is paramount in itself to proof positive that the author did not consider it the type of either. A careful weighing and consideration of the above problems leads to the conclusion that the Millerian synonym, *not the Gronovian,* is the type of *Pinus canadensis* L.

To sum up: *Pinus balsamea* L. of the 1st edition of the Species Plantarum is an aggregate which may be considered to include *all* of the firs, spruces, and hemlocks.

Miller, in 1759, segregated the Linnaean aggregate, recognizing four species, but did not name them under the binomial system.

Linnaeus, in 1763, recognized, in part, the work of Miller and established *Pinus canadensis,* on, we shall claim, the Millerian species (No. 5) but probably intended it to contain all species with *drooping* cones. Unfortunately he neglected to remove the Plukenetian synonym from *Pinus balsamea* which, very likely, was intended to include all species with *erect* cones. Five years afterward, 1768, Miller published the 8th edition of the Gardeners Dictionary and in this work he not only recognized the four

*Since writing the above I have received a communication from Mr. A. Gepp, of the British Museum, in which he mentions me that the plate of Miller referred to is considered by Mr. A. Bruce Jackson, an authority on the Compositae, to be the *Picea mariana* B.S.P., thus confirming the deductions above drawn.

species of the 7th edition, but the binomial system also and consequently gave specific appellations to the species.

The balm of Gilead fir or balsam fir (species No. 6 of the 7th edition) becomes *Abies balsamea*, species No. 3.

The white spruce fir (species No. 5 of the 7th edition) becomes *Abies canadensis*, species No. 4.

The black spruce fir (species No. 4 of the 7th edition) becomes *Abies mariana*, species No. 5.

The Hemlock fir (species No. 3 of the 7th edition) becomes *Abies americana*, species No. 6.

Nos. 4 and 6 are described as follows:

4. Abies (*Canadensis*) foliis linearibus obtusiusculis sub membranaceis. *The Newfoundland White Spruce Fir.*
Abies foliis piceae brevioribus, conis parvis biuncialibus laxis, Rand.

6. Abies (*Americana*) foliis linearibus obtusiusculis bifariam versis conis subrotundis. *The Hemlock Spruce Fir.*

A careful comparison of the descriptions of *Abies canadensis* Mill. and *Pinus canadensis* L. shows them to be identical in everything except the Gronovian synonym which Miller has removed from the Linnaean species and described and named as *Abies americana*. Under the Vienna Code, Articles 46 and 47 govern; the latter provides that in segregating a species, the specific name is retained for the element first published; and the former provides that where two or more groups are of the same date the author chooses and his choice cannot subsequently be modified. The conclusions we have arrived at from the above study are:

(1) Linnaeus published *Pinus balsamea* in 1753 and made it broad enough to include all east North American Abieteae with single leaves.

(2) Miller, in 1759, segregated the Linnaean aggregate, recognizing four species.

(3) Linnaeus, in 1763, retained *Pinus balsamea* and described *Pinus canadensis* (dividing the hemlock spruce and placing a part under each so that it can not be considered typical of either), thus recognizing only two of Miller's four species from America.

(4) Miller, in 1768, reëstablished his four species, and gave them specific appellations under the binomial system as follows: the balsam fir or balm of Gilean fir became *Abies balsamea;* the

white spruce, *Abies canadensis;* the black spruce, *Abies mariana;* and the hemlock spruce, *Abies americana.*

Under Articles 46, 47, 48, 50, and 51 of the Vienna Rules this choice of specific names by Miller for these plants can not be modified and the proper names and leading synonyms of the species are as follows:

Abies balsamea (L.) Mill. Gard. Dict. Ed. 8, No. 3. 1768.

Abies taxifoliis, odora, Balsami Gileadensis, Raii Hist. App. Mill. Gard. Dict. Ed. 7, No. 6. 1759.

Pinus balsamea L. Sp. Pl. Ed. 1, 1002. 1753; Ed. 2, 1421. 1763 (as to name only).

Picea balsamea Loudon, Arb. Brit. 4: 2339. *f.* 2240-2242. 1844.

Picea canadensis (L). BSP. Prel. Cat. N. Y. 71. 1888.

Abies piceae foliis brevioribus, conis parvis biuncialibus laxis. Rand. Mill. Gard. Dict. Ed. 7, No. 5. 1759; Figures, *pl. 1.* 1760.

Pinus canadensis L. Sp. Pl. Ed. 2, 1421. 1763 (as to synonym of Miller).

Abies canadensis Mill Gard. Dict. Ed. 8, No. 4. 1768.

Pinus alba Ait. Hort. Kew. 3:371. 1789.

Abies alba Michx. Flor. Bor. Amer. 2:207. 1803 (not of Miller, 1768).

Picea alba Link, Linnaea 15:519. 1841.

Picea mariana (Mill.) BSP. Prel. Cat. N. Y. 71. 1888.

Abies piceæ foliis brevibus, conis minimis. Rand. Mill. Gard. Dict. Ed. 7, No. 4. 1759.

Abies mariana Mill. Gard. Dict. Ed. 8, No. 5. 1768.

Pinus mariana Du Roi, Obs. Bot. 38. 1771.

Pinus nigra Ait. Hort. Kew. 3:370. 1789.

Abies nigra Du Roi, Handb. Baumg. 2:182. 1800.

Picea nigra Link, Linnaea 15:520. 1841.

Tsuga americana (Mill.) nov. comb.

Pinus balsamea L. Sp. Ed. 1, 1002. 1753; Ed. 2, 1421. 1763 (as to synonyms).

Abies minor, pectinatis foliis, Virginiana, conis parvis subrotundis, Pluk. Alm. Mill. Gard. Dic. Ed. 7, No. 3. 1759.

Pinus canadensis L. Sp. Ed. 2, 1421. 1763 (as to synonym of Gronovius).

Abies americana Mill. Gard. Dict. Ed. 8, No. 6. 1768.

Pinus americana Du Roi, Obs. Bot. 39. 1771.

Abies canadensis Michx. Fl. Bor. Am. 2:206. 1803 (not of Miller, 1768).

Picea canadensis Link, Linnaea 15:524. 1841.

Tsuga canadensis Carr. Trait. Conif. 189. 1855.

I wish here to thank Mr. A. Gepp, of the British Museum (Natural History), and Miss Mary A. Day, of the Gray Herbarium, most heartily for many valuable notes and kind assistance.

REPRINTS OF PUBLICATIONS FROM THE RESEARCH LABORATORY, PARKE, DAVIS & CO., DETROIT, MICH.

The present system of collecting reprints of articles published from the Research Laboratory was begun in 1912. Reprints of the following articles published subsequent to that time are available and will be sent upon request. The publications marked (*) are no longer available.

1. On the Administration of Diphtheria Toxin in a Collodion Sac. By E. C. L. Miller. (*Journal of Infectious Diseases,* Vol. 8, January, 1911, pp. 50-65.)

2. A Further Contribution to Our Knowledge of Insecticides—Fumigants. By Chas. T. McClintock, H. C. Hamilton and F. B. Lowe. (*Journal of the American Public Health Association,* Vol. 1, April, 1911, pp. 227-238.)

3. Duboisia Hopwoodii—A Histological Study. By Oliver A. Farwell. (Reprinted from *Merck's Report,* Vol. 20, May 1, 1911.)

*4. Etiology of Canine Distemper. By Newell S. Ferry. (*Journal of Infectious Diseases,* Vol. 8, June, 1911, pp. 399-420.)

*5. The Resistance of Smallpox Vaccine to the Coal-tar Disinfectants. By Chas. T. McClintock and Newell S. Ferry. (*Journal of the American Public Health Association,* Vol. 1, June, 1911, pp. 418-419.)

6. Production of Immunity with Over-Neutralized Diphtheria Toxin. By Chas. T. McClintock and Newell S. Ferry. (*Abdruck Aus Dem Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten,* Abt. 1, Originale, Bd. 59, July 15, 1911, pp. 456-464.)

7. Soaps from Different Glycerides—Their Germicidal and Insecticidal Values Alone and Associated with Active Agents. By H. C. Hamilton. (*Journal of Industrial and Engineering Chemistry,* Vol. 3, August, 1911, pp. 582-584.)

*8. The Sleepy Grass of New Mexico: A Histological Study. By Oliver A. Farwell. (*Merck's Report,* Vol. 20, October, 1911, pp. 271-273.)

*9. Some Observations on the Physiological Action of Sleepy Grass. By A. W. Lescohier. (*Merck's Report,* Vol. 20, October, 1911, pp. 271-275.)

*10. An Investigation of the Depressor Action of Pituitary Extracts. By Carey P. McCord. (*Archives of Internal Medicine,* Vol. 8, November, 1911, pp. 609-620.)

11. The Physiology of the Pituitary Gland and the Actions of Its Extracts. By Carl J. Wiggers. (*American Journal of Medical Sciences,* Vol. 141, April, 1911, pp. 502-515.)

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THE PROPER TIME TO COLLECT SANGUINARIA.

By O. A. Farwell.

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In the September issue of the *American Journal of Pharmacy* for 1913 there appeared a paper by Drs. Homerberg and Beringer on the proper time to collect Sanguinaria. The time suggested, "About or immediately after flowering," was based upon the results of assays of the drug "collected at various times from May—just after flowering—to August—just before the leaves began to die."

But as the time of collection of the samples assayed did not cover that period of the year specified by the U. S. P. for its collection, *i.e.*, "After the death of the foliage," it was thought desirable to make various collections during this period in order to supplement and make more complete the work carried out by Drs. Homerberg and Beringer. Accordingly, samples of the rhizome were collected at various times during the ensuing year which covered both the active and quiescent periods of the species. The rhizomes were carefully cleaned, the rootlets removed, and air-dried in the shade at ordinary room temperature; the last collection, however, was dried artificially. The rootlets were kept separately until the close of the experiment, when they were mixed together and assayed. They yielded 1.77 per cent *sanguinarine*, thus averaging about one-third the amount obtained from the rhizomes.

The results obtained confirm in all respects those obtained by Drs. Homerberg and Beringer, indicating that the best time to collect the rhizome, which should be freed of rootlets, is at the flowering season.

The commercial drug can be readily separated on gross internal characters into three grades, probably representing three species:

A. This grade breaks with a short, waxy fracture, showing a white ground plentifully sprinkled with red resin cells.

B. This grade breaks with a short fracture, showing a rather soft, more or less mealy surface of a brick-red or orange color, the resin cells not being perceptible to the naked eye.

C. This grade breaks with a short, waxy fracture, and shows a liver-brown or reddish-brown color.

The rhizomes collected for experimental work were of typical

Sanguinaria canadensis Lin., and corresponded to grade *A* as above outlined; the commercial drug assayed for comparison showed a higher percentage of alkaloid than that specially collected.

The assays were made by Mr. J. B. Williams, of the Scientific Laboratory.

ASSAY OF COMMERCIAL DRUG, SANGUINARIA.

Grade	Moisture, per cent.	Sanguinarine, per cent.
A	6.68	6.95
B	6.80	6.01
C	6.6	7.01

ASSAY OF COLLECTED SAMPLES OF AIR-DRIED SANGUINARIA.

Time of collection	Moisture, per cent.	Sanguinarine per cent.
11/13/13	79.84	4.75
1/16/14	78.71	4.70
3/18/14	84.24	4.84
4/16/14 (Flowering season)	85.54	6.53
5/28/14 (Fruiting season)	79.20	5.10
6/19/14 (After fruiting season)	76.50	5.00
7/30/14 (Just after death of foliage)	76.12	5.00
10/29/14 Artificially dried	79.88	4.93

ASSAY OF COLLECTED SAMPLES OF AIR-DRIED ROOTLETS OF SANGUINARIA.

Time of collection	Moisture, per cent.	Sanguinarine per cent.
November, 1913, to July, 1914	79.5	1.77

NOTES ON THE MICHIGAN SPECIES OF POLYGONATUM.*

Oliver Atkins Farwell.

(with plates 12-18.)

Much difficulty has been experienced, during the past few years, in trying satisfactorily to place all our forms of *Polygonatum*, known as Solomon's Seal, within the prescribed limits of the two species accredited in our manuals to North America. There are a number of characters which seem to be common to all. The stem is finely many-striate, cylindrical and smooth when green but channelled more or less deeply when dry; the leaves of all are glaucous beneath and have minutely pubescent or papillose margins, the papillæ of which range from 85 microns in *P. cuneatum* to 7 microns in *P. biflorum;* they are indefinitely nerved, the smallest having not less than fifty-five nerves, which can be definitely distinguished by the unaided eye; and they are never acute but end in a short, narrow or broad, very obtuse or rounded apex; the peduncles are compressed, channelled on one side, and arching; the pedicels, at least at the flowering season, are bracteate near their junction with the peduncle; the perianth-lobes are deltoid, dark green, and barbellate within; the filaments are partly adnate, partly free; the anthers are sagittate; the fruits are black with a bluish bloom, as in many species of *Vaccinium*, and if collected before maturity appear, in the dried specimens, to be indehiscent, but at full maturity they are dehiscent, rupturing with the slightest pressure; the bony, whitish or greenish white seeds are turgid, subreniform, and smooth. The forms can be definitely separated into two groups based upon pubescence of foliage or lack of it, size of flowers, and form of filaments, the two groups corresponding to the two species usually recognized. But it is next to impossible to include under one species forms with yellow flowers and those with green; forms that are constantly seven or

*Contributions to the Botany of Michigan, No. 11.

eight feet in height with those that never exceed one or two feet; forms that have elongated, very narrow leaves with those that have very short and broad ones; forms with slender flexuous peduncles with those having coarse, rigidly wiry ones. Differences in size alone are not characters upon which to base new forms of plants, but when correlated with other constant differences there is pretty good evidence for their recognition. An effort to place these forms led to an investigation of the publications of earlier botanists with some surprising and unexpected results.

It seems that neither Linnaeus, Miller, the elder Aiton, Murray, nor any of their contemporaries had recognized any American species of this group of plants nor even included American plants in the European species with which they dealt. Walter was the first to describe an American species, the *Convallaria biflora,* a glabrous plant with three-nerved leaves, which has since had a rather varied career. Bosc came next, describing *C. hirta,* a species with hispid peduncles and stems, otherwise glabrous. Michaux and Persoon referred the American species to the European *C. multiflora.* Wildenow followed with two new species, *C. pubescens* and *C. canaliculata.* Besides recognizing the above species under *Polygonatum,* now considered distinct from *Convallaria,* Pursh, suppressing Walter's specific name *biflora* and substituting for it his own name *angustifolium,* admitted *P. latifolium,* a European species, to a place in our flora. Poiret came next with *Convallaria parviflora.* The two Schultes described *C. commutata* and, in 1835, Dietrich added still another, *P. giganteum.* Thus in the first half century after the first American species had been described eight others were recognized by the earlier students of the American flora, seven being considered endemic and the other two identical with European species. It would thus seem that the botanists of a century ago had a more accurate conception of the genus in America than those of the present day. More than seventy years later Dr. Greene described three other species, *P. virginicum, P. boreale,* and *P. cuneatum,* bringing the total number of species described for America up to twelve; but these, like most of the others, have not been generally accepted as valid. Dr. Hooker, in 1840, united the nine species then known and placed them all under *P. multiflorum* as var.

Americanum. Dr. Torrey followed the lead of Hooker and went even further by uniting them all under *P. multiflorum*, not even giving them varietal rank. In the first edition of the Manual, Asa Gray recognized *P. pubescens* Pursh and *P. canaliculatum* Pursh. In the second edition, the former becomes *P. biflorum* Ell., the latter, *P. giganteum* Dietr., and a third species, *P. latifolium* Desf., is admitted. In later editions *P. commutatum* supersedes *P. giganteum* and *P. latifolium* is eliminated.

As stated above, Walter was the first to describe an American species under *Convallaria*, and his description is as follows:

biflora 2. foliis semiamplexicaulibus trinervis lævibus, oblongis, acutis, alternis; caule tereti lævi; pedunculis solitariis bifloris axillar, floribus flavescentibus.

Willdenow's descriptions, in part, of *C. pubescens* and of *C. canaliculata* are as follows:

Convallaria *pubescens*

Convallaria foliis alternis amplexicaulibus ovatis subtus pubescentibus, caule teretiusculo sulco exarto, pedunculis axillaribus subbifloris. . . .

Folia alterna ovata secunda basi leviter amplexicaulia integerrima nervosa, nervis 7 majoribus, supra saturate viridia glabra, subtus albicantia et ad nervos pilis albis obsita. Pedunculi uni- vel biflori secundi nutantes axillares. Corolla . . . albido-flavescens. . . .

Convallaria canaliculata foliis alternis amplexicaulibus oblongis margine pubescentibus, caule canaliculato, pedunculis bifloris axillaribus.

Differt a *Convallaria pubescenti:* foliis oblongis glabris margine tantum tenuissime pubescentibus, coralla magnitudine et facie Convallariæ Polygonati. Hanc sub nomine *Convallariæ multifloræ* in Flora boreali-Americana indicavit Michaux p. 202.

A very careful study of these descriptions never should have permitted any confusion as to the application of the names; if there are but two species in North America, then the proper names for them are *Polygonatum pubescens* (Willd.) Pursh, for the plant with pubescent leaves, and *P. biflorum* Walt. for the

plant with glabrous leaves. Willdenow's plate illustrating the former (see PLATE 12) is excellent and is exactly matched by plants in Michigan. Both *C. biflora* and *C. canaliculata* are described as having oblong leaves and two-flowered peduncles; in the former the flowers are described as *yellow* and in the latter as of *the size and appearance of those of C. Polygonatum*, which are *green* and about seven lines in length; the leaves in the former are said to be three-nerved, but Willdenow makes no mention of this feature; Kunth, however, in his description of Willdenow's plant says the leaves are ovate-oblong, about three inches long by sixteen or seventeen lines in width and striately many-nerved. The two cannot therefore be of the same species. Pursh described *P. angustifolium* with elliptical-lanceolate leaves; Elliott described *P. biflorum* Walt. likewise; in other respects these descriptions are essentially the same as that of Walter's *C. biflora*, each quoting the latter as a synonym. But an oblong leaf that is acute may be essentially the same as a leaf that is elliptical-lanceolate, and these three names and descriptions may, therefore, be considered as synonymous, Elliott restoring Walter's specific name, which had been suppressed by Pursh for one of his own coining.

It seems scarcely possible by the widest stretch of the imagination to include, under the above description of Walter, the pubescent-leaved plants with small greenish or greenish white flowers, yet that is not only what Gray and subsequent authors have done, but they have finally come to make the latter form the principal element of the species to which Walter's name has been applied or rather misapplied. The confusion of these species was started by Dr. Hooker, continued by Dr. Torrey, and finally completed by Dr. Gray, when he ultimately and inexcusably transferred the name of Walter from the species described by that author to an entirely different one and not of very close relationship. And this interpretation has been blindly followed by subsequent authors for nearly half a century.

The Michigan species naturally fall into two groups—one containing low, slender plants having pubescent chartaceous foliage and small flowers with slender filaments; and the other containing robust plants having glabrous, membranaceous leaves and large flowers with large, stout filaments. Both are to be placed

under Baker's section ALTERNIFOLIA. The first group may be known as the *Pubescentes,* and the second as the *Glabrata.* Under the *Pubescentes* three species have been described, *P. pubescens, P. cuneatum,* and *P. boreale.* In all these forms the filaments are papillate. Dr. Greene describes the peduncles of *P. boreale* as filiform and flexuous; this can scarcely be said of the specimens that have come under the author's observation, except as to the two or three uppermost, the others being too stout, compressed, and channelled to be called filiform; otherwise the specimens agree with Dr. Greene's descriptions. There is another form with the perianth pale green throughout or with the lobes just noticeably of a darker green than the tube.

In the *Glabrata* seven species have been described, *P. biflorum, P. hirtum, P. canaliculatum, P. parviflorum,* and *P. commutatum* (all originally as species of *Convallaria*), *P. giganteum,* and *P. virginicum;* two others have been referred to the European *P. latifolium* and *P. multiflorum,* making nine in all. These species will fall into two series, one with yellowish white flowers and relatively narrow leaves and the other with greenish flowers and relatively broad leaves. Several forms can readily be recognized; also one form with ancipital stems has been found, *i.e.,* in cross-section the outline is elliptical. *P. commutatum* and *P. giganteum* are but varying forms of *P. canaliculatum* and may better be considered as varieties of it. *P. virginicum* appears to be a broad-leaved form of *P. biflorum.* In Michigan another form is found which is analogous to *P. canaliculatum,* but the flowers are yellowish. In this group it would be natural to look for *P. parviflorum* Dietr. (*Convallaria parviflora* Poir.). Such descriptions (not the original) of this species which the author has seen point unmistakably to some species of the *Glabrata,* notwithstanding it is said to have flowers of the size of those of the *Pubescentes.* Probably the description was drawn from an immature dried plant and the flowers had not yet opened at the time of collection. Oftentimes the pressure exerted in course of pressing will burst open the buds so that they appear to be matured flowers in the dried specimens. *P. hirtum,* a species with glabrous leaves, but with the upper part of the stem and the peduncles hispidly pubescent, would also be sought here, but nothing answering to the description of either has been found in Michigan. No interme-

diate forms have come under the author's observation, *i.e.*, none of the large-leaved, large-flowered forms has had pubescent leaves or small flowers, nor none of the small-leaved, small-flowered forms has had gabrous leaves or large flowers. There appears to be no intergradation between the *Pubescentes* and the *Glabrata;* Walter's *P. biflorum* is typical of the latter, and Pursh's *P. pubescens,* of the former.

KEY TO THE SPECIES.

Leaves pubescent on the veins underneath; flowers 6-10 mm. in length; filaments filliform, papillate; plants up to 4.5 dm. in height (*Pubescentes*).
  Flowers with a yellowish white tube.
    Leaves ovate. *P. pubescens.*
    Leaves elliptical, cuneate. *P. pubescens cuneatum.*
  Flowers green, leaves elliptical.
    Leaves large, flowers dark green. *P. boreale.*
    Leaves small, flowers light green. *P. boreale australe.*
Leaves glabrous; flowers 12-25 mm. in length, filaments more or less flattened; plants taller and stouter, 6-24 dm. in height (*Glabrata*).
  Flowers yellowish, free part of filament smooth, longer than the anthers.
    Stems cylindrical.
      Leaves cuneate-lanceolate. *P. biflorum.*
      Leaves ovate- to oblong elliptical, flowers 12-14 mm. long. *P. biflorum virginicum.*
      Leaves ovate to lance-ovate, flowers 16-18 mm. long. *P. biflorum ovatum.*
    Stems ancipital. *P. ellipticum.*
  Flowers green, filaments granular, or papillate, free part shorter than the anthers.
    Peduncles two-flowered.
      Leaves lance-ovate, flowers 14 mm. long. *P. canaliculatum.*
    Peduncles two- to eight-flowered.
      Leaves ovate, flowers 12 mm. long. *P. canaliculatum americanum.*
      Leaves roundish ovate, flowers 14 mm. long. *P. canaliculatum giganteum.*

POLYGONATUM PUBESCENS (Willd.) Pursh, Fl. Am. Sept. 234. 1814.

Convallaria pubescens Willd. Hort. Berol. 45. *pl. 45.* 1810?

P. multiflorum var. americanum (in part) Hook. Flor. Bor. Amer. 2: 176. 1840.

P. biflorum Ell. in A. Gray, Manual, Ed 2, 466, 1856, mostly and of subsequent authors. Not Walter in Elliott, Bot. S. C. & Ga. 1: 393. 1817.

Salomonia biflora Farwell, Rep. Com. Parks Detroit 11: 53. 1900.

Stems glabrous, up to 4.5 dm. high, 2–4 mm. in diameter, leafless part the longer; leaves nine to thirteen, ovate to lance-ovate, 17–33 mm. wide by 5–7.5 cm. long, amplexicaul, subsessile, or short-petioled, green above, pubescent on the nerves below; three to seven of the nerves more or less prominent; peduncles short, about 12 mm. long, one- or two-flowered; pedicels shorter than the peduncle; flowers 8-10 mm. long by 2-3 mm. wide, occasionally sessile, cylindrical, tube yellowish white or white in dry specimens; the free part of the filament filiform, papillate, and shorter than the anthers; mature fruit globular, 8–10 mm. in diameter; seeds three to nine, 4 mm. wide. [PLATES 12, 13, A.]

Generally in rather dry woods and copses of oak and maple. MICHIGAN: Keweenaw Peninsula, June, 1886, *Farwell 380;* Rochester, May, 1914, *Farwell 3624.* MASSACHUSETTS: Russell, May, 1873, *H. H. Rusby* (distributed as *P. biflorum*). NEW JERSEY: Franklin, August, 1879, *H. H. Rusby* (likewise distributed as *P. biflorum*).

Polygonatum pubescens cuneatum (Greene) comb. nov.

P. cuneatum Greene, Leaflets 1: 181. 1906.

Differs from the species only in having longer and relatively narrower leaves, cuneate at the base (18–35 mm. wide by 6–12 cm. long). [PLATE 13, B.]

MICHIGAN: near Marquette, *Greene;* Detroit, May, 1895, *Farwell 380c;* Keweenaw Peninsula, October, 1914, *Farwell 3909.*

POLYGONATUM BOREALE Greene, Leaflets 1: 181. 1906.

Leaves larger, elliptical, 33–45 mm. wide by 7.5–10 cm. long, generally sessile; flowers green, darker than the foliage, otherwise as in *P. pubescens.* [PLATE 14, A.]

Copses of oak and maple. MINNESOTA: Winona, *Greene*. MICHIGAN: Keweenaw Peninsula, June, 1886, *Farwell 380a;* Ypsilanti, May, 1891, *Farwell 380b*.

Polygonatum boreale australe var. nov.

Leaves small (10–22 mm. wide by 2.5–5 cm. in length), elliptical or the lower inclined to ovate-elliptical; peduncles filiform, compressed only below the arch, one-flowered, flowers water-green (Ridgway's nomenclature), paler than the foliage. [PLATE 14, B.]

Sparsely wooded fields. MICHIGAN: Detroit, May, 1895, *Farwell 380d*.

POLYGONATUM BIFLORUM Walt. in Elliott, Bot. S. C. & Ga. 1: 393. 1817.

Convallaria biflora Walt. Fl. Car. 122. 1788.
Polygonatum angustifolium Pursh, Fl. Am. Sept. 234. 1814.
Polygonatum multiflorum var. americanum (in part) Hook. Flor. Bor. Am. 2: 176. 1840.

Whole plant glabrous, with nine to thirteen, secund elliptical-lanceolate leaves (18 mm. wide by 10–12.5 cm. long), rounded or somewhat cuneately narrowed to a sessile base, and with three to five more or less prominent nerves; peduncles slender, about 12 mm. long, two-flowered; flowers yellow; stems about 4.5 dm. high and 2–3 mm. in diameter. [PLATE 15, A.]

Atlantic seaboard, not typically represented in Michigan.

Polygonatum biflorum virginicum (Greene) var. nov.

Polygonatum virginicum Greene, Leaflets 1: 181. 1906.
Salomonia commutata (in part) Farwell, Rep. Com. Parks Detroit 11: 53. 1900.

Differing from the typical form of the species in its larger, ovate-elliptical to oblong-elliptical leaves, which are 25–55 mm. wide by 10–18 cm. long, with fifteen to twenty-three of the nerves more or less prominent; in its larger stems, 6–8 mm. in diameter, 6–9 dm. high, with the naked lower portion equal to or longer than the upper leafy part; in its larger flowers which are funnel-

shaped to linear-cylindric (4–6 mm. wide by 14–25 mm. long, even on the same plant), borne on longer (often three-flowered) peduncles (25–37 mm. in length), with subequal pedicels 6–10 mm. in length; fruit ovoid to globular, 12–16 mm. in diameter; seeds eight to ten. [Plate 15, B.]

Moist grounds in woods or in shady places. Virginia: *Greene*. Michigan: Belle Isle, Detroit River, June, 1893, *Farwell 1150b;* Parkedale Farm, June, 1914, *Farwell 3676, 3677, 3682, 3683*. The most developed form of the species.

Polygonatum biflorum ovatum var. nov.

Salomonia commutata (in part) Farwell, Rep. Com. Parks Detroit 11: 53. 1900.

Differs from the above in having smaller ovate to elliptical leaves (18–37 mm. wide by 7.5–10 cm. long), with fewer conspicuous nerves (seven to nine) and short stems (4–6 mm. in diameter and 4.5–6 dm. in length), often with a foliaceous, sheathing bract 10–12 cm. below the first leaf, and generally smaller flowers (4–8 mm. wide by 14–18 mm. long). [Plate 16, A.]

Open, rather dry woods and fields. Michigan: Belle Isle, Detroit River, June, 1893, *Farwell 1150a;* near Rochester, June, 1914, *Farwell 3674, 3678, 3679*.

Polygonatum ellipticum sp. nov.

Whole plant glabrous; stems about 9 dm. in height, the naked lower portion (3.5 dm.) *shorter than the leafy part (5.2 dm.) and ancipital, the cross-section being elliptical in outline (6 × 10 mm.),* whence the specific name; leaves about twenty, ovate-lanceolate (25–37 mm. wide by 7.5–10 cm. long), five to nine more or less prominent nerves, semi-amplexicaul, sessile; peduncles slender, up to 60 mm. in length with very unequal pedicels up to 25 mm. from four-flowered in the lower to one-flowered in the uppermost; flowers yellowish white, 16–20 mm. long by 4–5 mm. wide. [Plate 16, B.]

Dry fields and pastures. Michigan: Rochester, June, 1914, *Farwell 3673*.

POLYGONATUM CANALICULATUM (Muhl.) Pursh, Fl. Amer. Sept. 234. 1814; Kunth, Enumeration 5: 134. 1850.

Convallaria canaliculata Muhl. in Willd. Hort. Berol. 45. 1810?
Polygonatum multiflorum var. americanum (in part) Hook. Fl. Bor. Am. 2:176. 1840.

Whole plant glabrous; stems cylindrical, 6–10 mm. in diameter, about 10 dm. high, equally divided between the naked lower portion and the upper leafy part; leaves about fourteen, ovate to elliptical, 30–55 mm. wide by 10–14 cm., with nine to thirty-one more or less conspicuous nerves, semi-amplexicaul, subsessile or sessile; peduncle up to 30 mm. in length, with equal pedicels 12 mm. or less, two-flowered; flowers green, broadly tubular, 12–14 mm. long by 4–6 mm. wide. [PLATE 17, A.]

Moist elder thickets. MICHIGAN: Rochester, June, 1914, *Farwell 3677½*.

Polygonatum canaliculatum americanum (Hook.) comb. nov.
Polygonatum latifolium, Desf. in Pursh, Flor. Amer. Sept. 235. 1814.
Convallaria commutata J. A. & J. H. Scult. Syst. 7: 1671. 1830.
Polygonatum commutatum Dietr. in Otto & Dietr. Gartenz. 3: 223. 1835.
Polygonatum multiflorum var. americanum (in part) Hook. Fl. Bor. Amer. 2:176. 1840.
Polygonatum latifolium var. *commutatum* Baker, Jour. Linn. Soc. Bot. 11: 555. 1875.
Polygonatum biflorum commutatum Morong, Mem. Torrey Club 5: 115. 1894.

Stems 9–12 dm. in height, cylindrical, about 10 mm. in diameter, only the lower third naked; leaves eighteen to twenty-eight, ovate-lanceolate, 25–60 mm. wide by 7.5–14 cm., with nine to thirty-one more or less conspicuous nerves, peduncles often 5 cm. in length with subequal pedicels, 18 mm. or less, two- to eight-flowered (generally six- or seven-flowered on the lower peduncles); flowers 14 mm. long by 4 mm. wide. [PLATE 17, B.]

Low wet situations in open fields and thin woods. MICHIGAN: Ypsilanti, June, 1893, *Farwell 1150;* near Rochester, June, 1914, *Farwell 3675.* NEW JERSEY: Franklin, August, 1875, *H. H.*

Rusby (distributed as *P. giganteum*). Ontario: Walkerville, June, 1891, *A. L. Johnson* (likewise distributed as *P. giganteum*).

Polygonatum canaliculatum giganteum (Dietr.) comb. nov.

Convallaria multiflora L. in Michx. Fl. Bor. Amer. 1: 202. 1803.
Polygonatum multiflorum Desf. in Pursh, Fl. Amer. Sept. 234. 1814.
Polygonatum giganteum Dietr. in Otto & Dietr. Gartenz. 3: 222. 1835.
Polygonatum multiflorum var. americanum (in part) Hook. Fl. Bor. Am. 2:176. 1840.
Polygonatum biflorum var. giganteum Wood, Bot. & Flo. 346, 1870.

Stems 20 dm. or more in height, 18 mm. in diameter near the base, the lower naked portion about 9 dm. high; upper portion carrying about twenty-eight sessile or subsessile leaves, which are round-ovate or oval (30–37 mm. wide by 60–90 mm. long), with about fifty-three more or less conspicuous nerves; peduncles flat, 2 mm. wide by 90 mm. in length, rigid; pedicels 25 mm. or less, subequal; flowers usually four (two to five), 14–16 mm. long by 4–6 mm. wide; fruit 20 mm. in diameter ripening fifteen seeds, 5 mm. wide. [Plate 18.]

Moist elder thickets. Michigan: Rochester, June, 1914, *Farwell 3473*. The hyaline subulate bracts of the pedicels, which in the other species are small (2 mm. long) and early deciduous, are in this variety large (4–8 mm. long) and persistent, at least in some cases.

The author wishes to thank Miss Mary A. Day, of the Gray Herbarium, most heartily for transcripts of the original descriptions of Walter and Willdenow and for a sketch of Willdenow's plate of *C. pubescens* which is herewith reproduced for comparison; for a like purpose a photograph of the narrow-leaved plant *(P. biflorum)* collected by Dr. Rusby is also reproduced.

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EXPLANATION OF PLATES 12-18.

PLATE 12.

Polygonatum pubescens (Willd.) Pursh. From photograph of Willdenow's plate 45 in Hort. Berol.

PLATE 13.

A. *Polygonatum pubescens* (Willd.) Pursh. Photographs of specimens from Keweenaw Peninsula, *Farwell 380,* and from near Rochester, *Farwell 3021,* Michigan. B. *Polygonatum pubescens cuneatum* (Greene) Farwell. Photographs of specimens from near Detroit, *Farwell 380c,* and from the Keweenaw Peninsula, *Farwell 3909,* Michigan

PLATE 14.

A. *Polygonatum boreale* Greene. Photographs of specimens from Keweenaw Peninsula, *Farwell 380a,* and from near Ypsilanti, *Farwell 380b,* Michigan. B. *Polygonatum boreale australe* Farwell. Photograph of specimens from near Detroit, Michigan, *Farwell 380d.*

PLATE 15.

A. *Polygonatum biflorum* Walt. Photograph of a specimen from Franklin, New Jersey, *H. H. Rusby.* B. *Polygonatum biflorum virginicum* (Greene) Farwell. Photograph of specimens from Parkedale Farm, Michigan, *Farwell 3682.*

PLATE 16.

A. *Polygonatum biflorum ovatum* Farwell. Photograph of specimens from near Rochester, Michigan, *Farwell 3674.* B. *Polygonatum ellipticum* Farwell. Photograph of specimens from near Rochester, Michigan, *Farwell 3673.*

PLATE 17.

A. *Polygonatum canaliculatum* (Willd.) Pursh. Photograph of specimens from Parkedale Farm, Michigan, *Farwell 3677.* B. *Polygonatum canaliculatum americanum* (Hooke) Farwell. Photograph of specimens from near Rochester, Michigan, *Farwell 3675.*

PLATE 18.

Polygonatum canaliculatum giganteum (Dietr.) Farwell. Photographs of specimens from Parkedale Farm, Michigan, *Farwell 3478.*

POLYGONATUM PUBESCENS (WILLD.) PURSH.

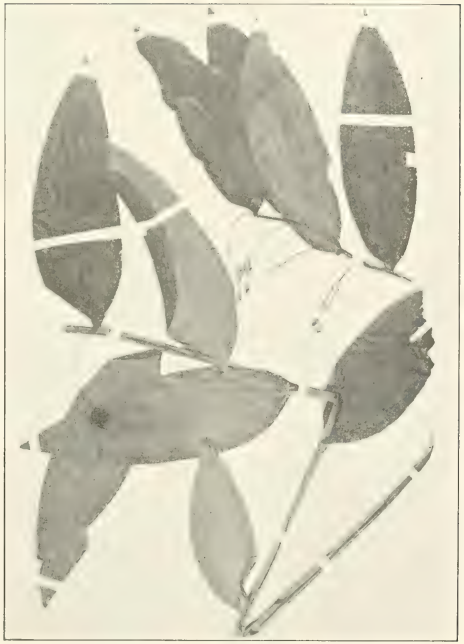
A. POLYGONATUM PUBESCENS (Willd.) Pursh.

B. POLYGONATUM PUBESCENS CUNEATUM (Greene) Farwell.

A. POLYGONATUM BOREALE Greene.

B. POLYGONATUM BOREALE AUSTRALE Farwell.

A. POLYGONATUM BIFLORUM Walt.



B. POLYGONATUM BIFLORUM VIRGINICUM (Greene) Farwell.

A. POLYGONATUM BIFLORUM OVATUM Farwell.

B. POLYGONATUM ELLIPTICUM Farwell.

A. POLYGONATUM CANALICULATUM (Muhl.) Pursh. B. POLYGONATUM CANALICULATUM AMERICANUM (Hook.) Farwell.

POLYGONATUM CANALICULATUM GIGANTEUM (Dietr.) Farwell.

BELLADONNA AND HYOSCYAMUS.

By Oliver A. Farwell,

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Much has been written of late about the cultivation of belladonna and hyoscyamus for commercial purposes. It has been shown that belladonna is hardy as far north as New York. Henbane is a much hardier plant and is known to be well established on Mackinac Island, in the Straits of Mackinac, between the two peninsulas of Michigan, and on the adjacent mainland on either side. Belladonna is hardy at Detroit, where it maintained a foothold for many years on ballast grounds until exterminated by the processes of economic improvements. It has also been under cultivation for several years, and is still in a flourishing condition, having weathered the cold winters of zero temperature and below without any protection and seemingly without injury to the vigor of the plants.

Seeds of the annual *Hyoscyamus Bohemicus* obtained from commercial drug, together with seeds and seedlings of *Atropa Belladonna* and of the biennial *Hyoscyamus niger* procured several years ago from the Department of Agriculture, were sown and transplanted, and these or their descendents are still producing flourishing growths. The seeds of belladonna sown in the garden did not germinate, but the self-sown seed from the plants germinated the following spring in large numbers. Individuals of the biennial henbane often have corollas that are veined with brownish-green or olive instead of violet or purple, even on the same plant, and the contrast is rather striking.

In view of the fact that the henbanes are subject to destructive attacks by the common potato bug, *Doryphora decemlineata,* and the allied, three-lined potato-bug, *Lema trilineata,* it would seem that its cultivation for commercial purposes in this country will not meet with any degree of success, as the cost of keeping the plants free from these pests would make the price of the drug prohibitive. Belladonna is not so liable to be attacked, last year (1914) being the first season since their cultivation began (1910) that these plants were infested by insect pests.

In a recent paper on belladonna and hyoscyamus, published in this Journal by Professor Newcomb, of the Minnesota Col-

lege of Pharmacy, *Hyoscyamus albus* is illustrated by two figures. From a taxonomic point of view, at least, these figures, as representative illustrations of *Hyoscyamus albus* Lin., are open to

[illegible] reproduction of Plate 2 in vol. xx Reichenbach's Icones Florae [illegible] et Helveticae. I, *Hyoscyamus albus* L.; II, *Hyoscyamus niger* L.; III, [illegible] *pallidus* Koch. 1, [illegible], ut videas aestivationem [illegible]; 2, [illegible]; 3, Fructus transsectus vides operculum pyxidis; 4, [illegible]; 5, 6, Semina [illegible]; 7, Area testae.

criticism. If compared with the accompanying figure, which is a reproduction of plate 2 of vol. 20 of Reichenbach's *Icones*, showing *H. niger*, *H. albus*, and *H. pallidus*, it will at once be seen that they show no strain of *H. albus*, a species more closely related to *H. aureus* than to *H. niger*. *H. albus* differs widely

in its nearly *orbicular* leaves, all of which are *petioled,* and in its *prominently peduncled flowers* and *fruits,* the *calyces* of which are of a different shape; none of these characters appear in the figures referred to, which, however, do compare very favorably with that of *H. pallidus,* and this, it is very evident, is what they represent. Undoubtedly Professor Newcomb has placed too much reliance upon the authenticity of the nomenclature adopted by seedsmen, for his figure of *H. albus* shows that he has received seed improperly named, a state of affairs which is not at all uncommon in the trade.

Professor Newcomb's experiments developed no tendency in the biennial hyoscyami to become annual or *vice versa,* which is in accordance with my own observations covering a period of several years. These species might, therefore, be better understood if the annual and biennial forms are maintained as distinct species. Under these conditions, *Hyoscyamus niger* Lin. will be restricted to the large, branched, biennial plant having yellow flowers, with violet, purple, or brownish-green veins. The annual plant, with similarly colored flowers, but with a slender, generally unbranched stem, will then be known as *H. Bohemicus* F. W. Schmidt, of which the yellow-flowered *H. pallidus* Wald. and Kit. becomes a color variety.

The proper names and leading synonyms are as follows:

Hyoscyamus niger Lin. Sp. Pl. 179, 1753. Probably belonging here are:

H. officinarum Crantz Inst. 2, 325, 1766.

H. lethalis Salisb. Prod. 131, 1796.

Hyoscyamus Bohemicus F. W. Schmidt, Fl. Bohem. 3, 31, 1795.

H. Verviensis Lejune, Fl. de Spa. 1, 116, 1811.

H. agrestis Kit. in Schult. Œster, Fl. Ed. 2, 1, 383, 1814.

H. pictus Roth Nov. Pl. Sp. 119, 1821.

H. niger Lin. var. *annua* Sims. Bot. Mag. t. 2394, 1823.

H. niger Lin. var. *agrestis* Nees ab Es. Trans. Lin. Soc. 17, 77, 1837.

Hyoscyamus Bohemicus Schmidt var. pallidus (Wald. and Kit.) N. Comb.

H. pallidus Wald. and Kit. Plant. Rar. Hung. ex Willd. Enum. Hort. Berol. 227, 1809.

H. niger Lin. var. *pallidus* Koch Syn. 509, 1837.

NOTES ON MICHIGAN LILIACEAE.*

BY OLIVER ATKINS FARWELL.

[WITH PLATE 20]

NEW VARIETIES OF ALLIUM CANADENSE.

In Michigan there are three well-defined races or varieties of the common wild garlic, *Allium canadense* L. The type with narrow leaves and numerous, small, ovoid, whitish, obtuse or acutish bulblets in the simple umbel; a form with noticeably broader leaves but with fewer, larger, long-acuminate bulblets which are red at maturity; and a larger, glaucous form with more fleshy leaves, often with two or three sessile, contiguous umbels, which bear a larger number of obovoid or nearly spherical bulblets of a yellowish-white color. There is such a marked difference in the appearance of these forms, at least in the living state, that it seems advisable to name them and place them on record.

Allium canadense ovoideum var. nov.

Bulb ovoid, about 19 mm. long, outer coats fibrous-reticulated, 5-8 cm. below the surface; plant 3-4 dm. high, green, with four or five leaves near the base, these equaling the scape or a little shorter; umbel terminal, mostly of a few, twelve or less, large, ovoid-acuminate, sessile bulblets with or without a few long-pedicelled flowers and some secondary umbels of one to three bulblets, on long rays 5-10 cm. long; involucre of one to three ovate, acuminate, scarious bracts, 2.5-4 cm. long; bulblets of the umbel gradually tapering from a broad base, the larger about 22 mm. in length, mostly rose colored at maturity; generally there are no flowers, but some umbels may have from one to four, and occasionally there may be one in one of the umbellets; the flowers are pale purple, on pedicels 5 cm. in length, 8 mm. across when open, 5-6 mm. high; segments acute, the outer narrowly ovate, the inner oblong or linear.

On wet banks in open fields. MICHIGAN: near Rochester, June 11, 1914, *Farwell 3667*.

*Contributions to the Botany of Michigan, No. 12.

Differs from the typical form of the species in its large long-acuminate, rose-colored bulblets, in the narrower perianth-segments and longer pedicels.

Allium canadense robustum var. nov.

Bulb spherical or nearly so, 2.5 cm. in diameter or less, the outer coats fibrous-reticulated, deep-seated, 15-18 cm. below the surface; scapes, often two, 3-4.5 dm. in height, 6 mm. or less in diameter, and, with the two to six leaves near the base, glaucous; leaves rather fleshy, 6 mm. wide, channelled above, convex below, two-thirds to three-fourths the length of the scape; scape bearing one to three sessile, contiguous umbels, mostly of bulblets, at its apex with one or more rays, 12.5 cm. or less in length, each bearing an umbellet of from one to three bulblets; bulblets often foliaceous, from spherical or nearly so to obovoid, tipped with a minute curved point, the larger about 12 mm. in longest diameter, very numerous, often more than thirty, yellowish-white; involucre one to four ovate, acuminate scarious bracts, the acumination often prolonged to a length of 7.5 cm.; flowers, when present, few, on pedicels 19-38 mm. long, white or pale rose, 7 mm. high, 10 mm. across when open, segments obtuse, the outer ovate, the inner oval or obovate.

In rather moist meadow lands. MICHIGAN: near Rochester, June 9, 1912, *Farwell 2629;* June 13, 1912, *Farwell 2729;* June 11, 1914, *Farwell 3666.*

Differs from the typical form of the species in its more robust habit, compound umbel with differently shaped bulblets, obtuse petals and general glaucousness. Listed as *Allium rubrum* Osterhaut? in Rpt. Michigan Acad. Sci. 15: 169. Nov. 1913.

NEW SPECIES OF LILIUM.

I have long considered that the wild red lily of the middle west is specifically distinct from the yellow-flowered *Lilium canadense* L. of the Atlantic seaboard.

Our plant is much taller and coarser; the flowers generally are strongly revolute and red instead of yellow; if the two plants were specifically the same, it would be reasonable to expect to see a yellow-flowered individual at times in the middle west, but such has never come under my observation during the twenty-five years I have been observing these plants. I had become so thoroughly

imbued with the idea that our red lily of the middle west was the true *Lilium canadense* that when I first saw the smaller, yellow-flowered lily east of the Appalachians, from the window of a slowly moving train, I was unable to recognize it as of that species, it appeared to be so radically different from my conception of what *Lilium canadense* should be. The red-flowered plant is unquestionably a distinct species.

Lilium michiganense sp. nov.

Leaves remotely whorled, six to ten in a whorl, three- to seven-nerved and rough on the nerves beneath as well as on the margins, lanceolate (12 mm. wide by 9 cm. long) to ovate-lanceolate (19 mm. wide by 4.5 cm. long); flowers in a pyramidal cluster (two to four axial from the uppermost whorl and about four racemosely disposed on the terminal portion of the stem), the peduncles 10-12 cm. long, often bearing a foliaceous bract near the middle.

Michigan: Wiard's Crossing, July 9, 1910, *Farwell 2162*.

Similar to *L. canadense* in foliage and to *L. superbum* in its flowers, which are of a beautiful orange-red, copiously spotted inside with purplish-brown or crimson spots. The upper leaves of this plant are often smooth on the veins beneath, a transition to *L. superbum*, which, though credited to Michigan, I have not yet detected here. The new species occurs in three well-defined forms, and I have taken the most highly developed form, although not the commonest, as the type.

Lilium michiganense umbelliferum var. nov.

Differs in having the stem end abruptly at the uppermost node, the inflorescence being composed of an umbel only, of from two to five flowers, from the axils of the leaves of the uppermost node.

Michigan: Wiard's Crossing, July 9, 1910, *Farwell 2162⅓*; Birmingham, September 7, 1903, *Farwell 1261c;* Belle Isle, July 16, 1892, *Farwell 1261;* Palmer Park, July 16, 1902, *Farwell 1261b;* Rochester, July 4, 1896, *Farwell 1261a.*

Lilium michiganense uniflorum var. nov.

The simplest form, in which the stem is continued beyond the uppermost whorl of leaves and bears a single, nodding flower.

MICHIGAN: Wiard's Crossing, July 9, 1910, *Farwell 2162¼*; Rochester, July 14, 1912, *Farwell 2848;* Parkedale Farm, October 5, 1913, *Farwell 3523;* Rochester, July 14, 1913, *Farwell 2848.*

It is a misnomer to call *L. michiganense,* as is usually done here, "the wild yellow lily," as the flowers are never yellow; the buds are at first green, then yellow (some, however, never show any sign of yellow externally), and finally red; the flowers when opened are orange-red externally and on the blade internally, the midvein being orange-yellow, the claw pale yellow or whitish and copiously blotched with crimson spots which extend upward on the blade for one-half to two-thirds its length. I have included in this species certain forms in which the buds show no yellow color, and the flower has brownish-purple instead of crimson spots with orange-red extending down the claw, but in which the leaves are characteristic. Further study may prove these forms to be distinct. The segments are recurved to below the middle, often spirally coiled, so that the apex is again ascending.

Lilium peramoenum sp. nov.

Similar to *L. michiganense,* but the leaves are more numerous, eight to sixteen in a wheel, with a corresponding increase in the number of flowers in the inflorescence; the flowers are orange-red throughout, dotted with copious but smaller spots; the leaves are narrower, linear-lanceolate, 10 mm. wide by 9 cm. long to oblong-lanceolate 15 mm. wide by 7 cm. long.

MICHIGAN: Parkedale Farm, July 19, 1914, *Farwell 3726.* Elder thickets in rich muck lands. *L. michiganense* is found usually in poorer soil, though it may be in dry fields and on banks or in wet swamps and meadows. Both species range from 1-2 m. in height.

NOTES ON UNIFOLIUM BIFOLIUM.

In Rhodora for December, 1914, Mr. Fernald describes a pubescent form of *Maianthemum canadense* as a new variety (var. *interius*) and gives its range from Illinois north and northwestward into Canada. He had not seen this pubescent form east of Illinois or Wisconsin. The late Mr. G. H. Hicks collected it at Owosso, Michigan, in 1889, and I found it at Stoney Creek,

Michigan, in 1913. Both stations are in the southeastern part of the State, about sixty miles apart.

A careful study of a series of specimens, ranging from Oregon to Hungary, allows of but one conclusion—that there is but a single species and that the plant recently described by Mr. Fernald as *Maianthemum canadense* var. *interius*, is, in reality, identical with the Linnean *Convallaria bifolia*, and is, consequently, *Unifolium bifolium* (L.) Greene. The plant from the Black Hills, Figs. 7, 8, it will be observed, corresponds with that from Denmark, Fig. 6; the collections of Mr. Hicks, Figs. 9, 10, are nearly identical with those from Hungary and Bavaria, Figs. 1, 2; and my own collection from Stoney Creek, Fig. 11, is very close to another plant, Fig. 3, from Bavaria; the outlines of the leaves of the var. *canadense*, Figs. 12-19, are the same as those of the type, no other difference, save that of pubescence, being detectable; the apex in both is acute or obtuse, the base cordate or sagittate; the western variety *kamtschaticum*, Figs. 22, 23, shows the broadest sinus; the European type, the deepest; the var. *canadense*, the shallowest; and the var *ovale*, Figs. 20, 21, the narrowest; but there is a regular graduation from one extreme to another. The var. *kamtschaticum* has the longest petiole with the blade prominently decurrent on it; the plants of Loher, Fig. 3, and Cavassius, Fig. 4, show the blades slightly decurrent on the petioles, thus in a measure paralleling the western form. The pedicels vary from 2-6 mm. in length in all the forms; the petioles of the upper leaf measure 1-6 mm., and of the lower leaf, 2-16 mm., in all the forms except the western, which has much longer petioles. There is in Michigan a plant with broadly ovate or oval leaves, Figs. 20 (stem-leaf), 21 (root-leaf); Pursh traversed the region of "the Lesser and Great Lakes," and I have no doubt that this form is the basis of his *Smilacina canadensis* var. *ovalis;* the base of the leaf is cordate or rather sagittate, but the sinus is closed or nearly so, which renders it inconspicuous. There is a form which has three leaves to the stem and in Europe forms are found with but one leaf. The differences in length of petioles, pedicels, and the size of the leaf-sinus cannot be correlated with other characters with a sufficient degree of accuracy to warrant separating the different forms as species; such differences as exist are of degree and not of kind and therefore are not of specific value. The species and its forms may be listed as follows:

Unifolium bifolium (L.) Greene

Maianthemum canadense var. *interius* Fernald, Rhodora 16: 211. 1914.

Michigan: Owosso, May 21, 1889, *G. H. Hicks;* Stoney Creek, May 25, 1913, *Farwell 3412.* Illinois westward to the Black Hills and northward into Canada; also in Europe.

Unifolium bifolium monophyllum forma nov.

Differs from the species only in having but one leaf on the stem. Sweden: Moheda, *C. G. H. Cavassius,* in the herbarium of Parke, Davis & Company.

Unifolium bifolium canadense (Desf.) comb. nov.

Maianthemum canadense Desf. Ann. Mus. Paris 9: 54. 1807.

Convallaria bifolia var. *canadensis* Poir. Enc. 4: 371. 1816.

Michigan: Detroit, May 9, 1895, *Farwell 379a;* Algonac, September 13, 1914, *Farwell 3898.* From Michigan eastward, ranging north to Newfoundland and south to the Carolinas.

Unifolium bifolium trifolium (Pursh) comb. nov.

Smilacina canadensis var. *trifolia* Pursh, Fl. Am. Sept. 233. 1814.

The stem has three leaves, otherwise like the variety *canadense.*

Michigan: Detroit, May 9, 1895, *Farwell 379b.*

Unifolium bifolium ovale (Pursh) comb. nov.

Smilacina canadensis var. *ovalis* Pursh, Fl. Am. Sept. 233. 1814.

I here adopt Pursh's varietal name for the form in the Lake Superior district, with broadly ovate or oval leaves.

Michigan: Keweenaw Peninsula, June, 1886, *Farwell 379;* October, 1914, *Farwell.*

Unifolium bifolium kamtschaticum (Gmel.) Piper

California to Idaho and Alaska; also Siberia.

NOTES ON VAGNERA

Vagnera stellata (L.) Morong

The common woodland form, 3-4.5 dm. in height, bearing seven to twelve leaves with a short, harsh pubescence on the veins on the lower surface, becoming, with age, glabrate or smooth, at least to the touch.

Michigan: Ypsilanti, May 29, 1891, *Farwell 1121;* Parkedale Farm, May 19, 1912, *Farwell 2567;* Rochester, June 28, 1914, *Farwell 3099.*

This I take to be the typical form of the species. There is a wide range in the size of the plant and leaves, in the pubescence, and in the habitat of this species; the rhizome seems to vary in size correspondingly; the fruit, while young, is green; but as it approaches maturity it becomes purple on the angles; then intermediate lines of a paler color appear; later it is finely lined or spotted and ultimately becomes a ruby red as in *V. racemosa* and the other species of the genus. Fruit, however, in this species is a rarity; most of the flowers are sterile and drop from their pedicels at an early stage as though the plant were of hybrid origin; if such is the case the parents probably are *V. racemosa* and *V. trifolia.*

Vagnera stellata mollis var. nov.

Differs from the typical form of the species in having the leaves densely and permanently velvety pubescent all over the lower surface; in the more numerous leaves, six to fourteen, 1-5 cm. wide and 3.5-20 cm. long; plant often larger, attaining a height of nearly 1 m., but sometimes smaller and not exceeding 18 cm.

Michigan: Parkedale Farm, May 30, June 11, and July 4, 1914, *Farwell 3651, 3669½, 3720½;* growing in muck lands, on barren hilltops, and in *Sphagnum,* in the order named. South Dakota: Black Hills, *W. S. Rusby.*

The habitat of the variety is as variable as that of the typical form. The plants growing in *Sphagnum* are the smallest but seem to perfect fruit more readily than those in other situations; those growing in rich muck in elder thickets are the largest and do not perfect fruit at all; the plant does not disdain the exposed tops and sides of more or less barren hills, but fruit is seldom seen in

such localities. With all its variableness, however, the soft velvety pubescence of the plant remains constant.

Vagnera trifolia (L.) Morong

This species and *Unifolium bifolium* are locally known as wild lily-of-the-valley. In the Lake Superior region of Michigan both are quite common. Besides the ordinary three-leaved form of *V. trifolia* there are two others that are frequently met with; one has two leaves to the stem, and the other, one leaf. These may be recorded as follows:

Vagnera trifolia bifolia forma nov.

A form with two leaves on the stem.

Michigan: Keweenaw Peninsula, June 16, 1886, *Farwell 378a.*

Vagnera trifolia unifolia forma nov.

A form with only one leaf on the stem.

Michigan: Keweenaw Peninsula, June 16, 1886, *Farwell 378b.*

Department of Botany,
Parke, Davis & Company,
Detroit, Michigan.

Explanation of plate 20.

Figs. 1-11. Unifolium bifolium (L.) Greene.

1. Pressburg, Hungary, *Richter.* 2. Woods near Munich, Germany, May, 1891, *C. J. Mayer.* 3. Woods near Munich, Germany, May, 1887, *Loher.* 4. Moheda, Sweden, *C. G. H. Cavassius.* 5. Same locality and collector (forma *monophyllum*). 6. Lyngby, Denmark, June, 1865, *J. Lange.* 7, 8. Black Hills, South Dakota, *W. S. Rusby.* 9, 10. Owosso, Michigan, May 21, 1889, *G. H. Hicks.* 11. Stoney Creek, Michigan, *Farwell 3412.*

Figs. 12-19. Unifolium bifolium canadense (Desf.) Farwell.

12-14. Westfield, Massachusetts, May 29, 1873, *H. H. Rusby.* 15. East Greenwich, New York, 1867, *A. Fitch.* 16, 19. Algonac, Michigan, September 13, 1914, *Farwell 3898.* 17, 18. Detroit, Michigan, May 9, 1893, *Farwell 379a.*

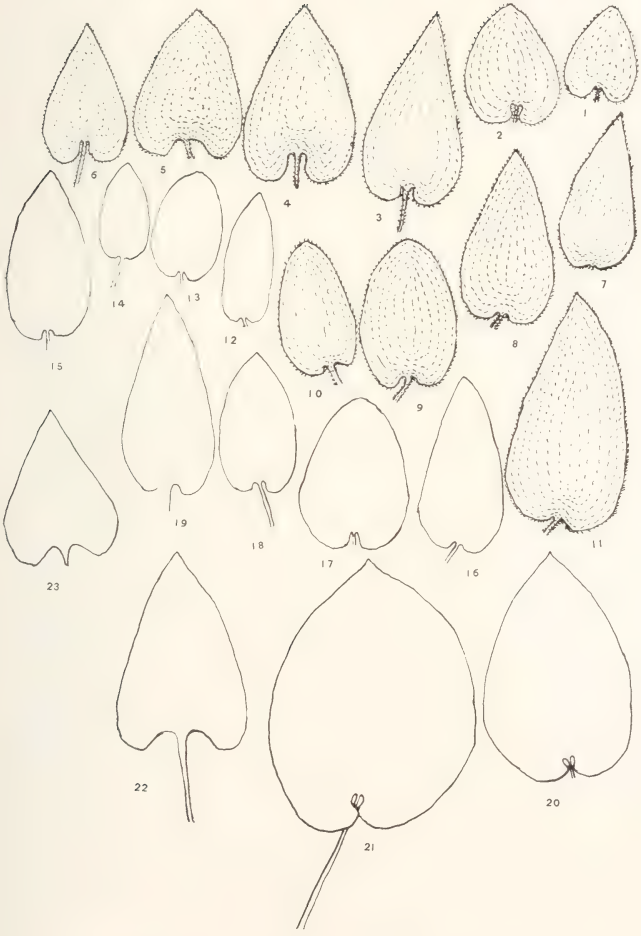
Figs. 20, 21. Unifolium bifolium ovale (Pursh) Farwell.

20. Lower leaf; Keweenaw Peninsula, Michigan, June 16, 1886, *Farwell 379.* 21. Root leaf; same locality and collector, October, 1914.

Figs. 22, 23. Unifolium bifolium kamtschaticum (Gmel.) Piper.

22. Lower leaf; Cascades of the Columbia River, Washington, June 3, 1882, *W. N. Suksdorf 23.* Upper leaf; same locality, collector, and date.

Figs. 1-8, 12-15, 22, and 23 were drawn from specimens in the herbarium of Parke, Davis & Company; the remaining figures, from specimens in the herbarium of the writer. All are reduced one-half.



UNIFOLIUM BIFOLIUM (L.) GREENE

91174

THE HEMLOCK SPRUCE.

OLIVER A. FARWELL.

(Department of Botany, Parke, Davis & Co., Detroit, Mich.)

In Rhodora for March, 1915, Mr. Alfred Rehder published a criticism of my paper on "the correct name of the Hemlock Spruce" which appeared in the issue of the Bulletin of the Torrey Botanical Club for December, 1914. I shall not attempt to answer the salient points of his discussion in the order in which they are given, but will take analogous but non-contiguous features, and bring them together in order to show as clearly as possible the inconsistencies and fallacies of his statements and conclusions.

In dealing with specific names and the species which they represent two axioms are in general use. The first is that any species which has had the type specifically mentioned or designated by the author stands or falls with that type; the author's specific name cannot be transferred to another plant. The other is that where the type has not been specifically mentioned or designated, the first author revising the species must of necessity make his own choice as to which element shall bear the name. That choice should be, and perhaps is, generally, determined by the internal evidence.

Mr. Rehder fails to see wherein my reference to Article 46 of the Vienna Rules bears upon the case at issue since the Article mentioned treats of the combining of two or more species and not of the division of one. The Vienna Rules are general laws for the guidance of such botanists as have subscribed to them. In the treatment of species, the first author revising them is given, under certain conditions, the choice of making his own interpretation as to the application of the specific names, and subsequent revisers cannot alter this interpretation. The Vienna Congress in handling this subject relating to the treatment of species first considers the combining of species, and it is here that the general law making the author's choice of name, under certain conditions, permanent, is expressed. When considering the division of a species, the Congress, acting upon the basis that "brevity is the soul of wit," declined, and justly so, to perpetrate a needless repetition.

In regard to the detailed description of *Pinus Balsamea* Linnaeus, which Mr. Rehder fails to see is not restrictive, it may be

remarked that the leaves of *Tsuga caroliniana,* a species growing in Virginia, may be notched at the end, thus coming under the designation *sub-emarginatis.* Also that the leaves of *A. Fraseri* may be either emarginate or obtuse. Rehder claims that it had not been discovered at the time *P. Balsamea* was published. It would be more accurate to say that it was not *recognized* at the time as a *distinct species* but there is no evidence to prove that it was not known and included in *Pinus Balsamea.* It must therefore be considered in any discussion of the subject. The leaves of the Balsam Fir from Vermont show an emarginate apex, but those from the Lake Superior district have no such markings but are rounded and as obtuse as the leaves of the Hemlock. The leaves of the Hemlock Spruce are as broad as those of the Balsam Fir, so they are *not excluded from consideration* by a comparison of the latter with those of the Silver Fir. The white bands on the under side of the leaves in the Hemlock are usually composed of four rows of stomata, but frequently are of five or six and sometimes of seven or eight; those on leaves of the Balsam Fir of Lake Superior are generally of seven or eight rows, but are frequently of any number between four and eight inclusive, while those on trees from Vermont from three to eight with six about the general run. It will therefore be seen from the foregoing that the Linnaean detailed description of *Pinus Balsamea* is not only not characteristic, for the leaves may be entire and obtuse and the rows of stomata as low as three, but it is broad enough to include the leaves of what are now considered as four species included under two genera. Not only that but the real characters, found in the cones, upon which the genera and species are separated, are not even touched upon by Linnaeus. The Linnaean description may, therefore, mean any one of two or more species and *Pinus Balsamea* Linn., as to the specific name, is the Balsam Fir; as to the description, an undefinable aggregate; and as to the synonyms, the Hemlock Spruce.

Rehder claims that the Gronovian synonym, the Hemlock Spruce, is the type of *Pinus canadensis* Linn. because the Linnaean diagnosis "is taken nearly literally from the synonym of Gronovius." Further on he admits *Abies canadensis* Miller to be a new name for a different species because "Miller does not quote *Pinus canadensis* Linnaeus as a synonym." Miller does not quote

the binomial, it is true, but he *does use the Linnaean specific name* and *he does use the Linnaean diagnosis* upon which Rehder lays so much stress and which "is taken nearly literally from the synonym of Gronovius. This shows as clearly as if" Miller "had expressly designated the Gronovian plant as the type of his species, that his" *Abies canadensis* "is based primarily on the plant described by Gronovius." In other words, if the Linnaean diagnosis is the type of *Pinus canadensis* to the exclusion of other matter not conspecific with it, the same must be true of Miller's *Abies canadensis,* for the diagnosis and the specific name are the same in each and have the same origin, thus making the two binomials synonymous even though Miller did not quote *Pinus canadensis* as a synonym. Rehder, therefore, fails to prove that *Abies canadensis* Miller is different from *Pinus canadensis* Linnaeus. Furthermore, since he insists that the Hemlock Spruce is the type of the latter it must also be the type of the former because the two, according to his own method of reasoning, have been proved to be synonymous. The fallacy is so evident that it needs no comment.

Rehder doubts that Miller intended to transfer the Linnaean species from *Pinus* to *Abies* and that if he actually had such intention he misapplied the name under the laws of priority. The only law of priority that will apply here is the one giving the first author revising a species the privilege of choosing the specific name under certain conditions—Article 46 which, by inference, covers the division of species as well as the combination of them. *Pinus canadensis* Linn. *is an aggregate without a designate type* consisting of the White Spruce and the Hemlock Spruce. In transferring from *Pinus* to *Abies* Miller separated the two elements, retaining the specific name and diagnosis for the White Spruce (the synonym of Miller) and giving a new name *Abies americana* to the Hemlock (the synonym of Gronovius). It is, therefore, very evident that Miller not only knew what he was about, but that he intended to transfer the species and that the name was not misapplied since he used it in the sense that Linnaeus did—*"canadensis" being indicative of the White Spruce,* as *Balsamea is of the Balsam Fir.* Under the above mentioned Article this choice cannot be changed. As above shown Rehder completely fails to prove that the specific name *"canadensis"* was

misapplied by Miller; he admits that *Abies canadensis* is the White Spruce, yet refers the *Pinus canadensis, a synonym,* to the Hemlock Spruce; the fallacy of Rehder's argument is very apparent.

The whole discussion revolves about the determination of a type for *Pinus canadensis* Linnaeus. If it can be shown that Linnaeus actually had the Hemlock Spruce in view for his *P. canadensis* it must be considered the type, and in this case it must be admitted that Miller has misapplied the name. But did he? Will Mr. Rehder admit that Miller had the Hemlock in view for his *A. canadensis* because he used the Linnaean diagnosis, which "was taken almost literally from the synonym of Gronovius?" Certainly not! Nor any one else! Then why for *P. canadensis?* In the first edition of the Species Plantarum Linnaeus placed two Hemlock synonyms under *P. Balsamea;* in the second edition he admitted another species, *P. canadensis,* to include the White Spruce and one of the synonyms (the more recent) of the Hemlock Spruce, leaving the other (the older) where originally placed, under *P. Balsamea.* When Linnaeus used these synonyms he gave them the status of post-Linnaean publications, and the older of these in point of actual publication, that of Plukenet, must therefore, under the law of priority, be considered to be the type of the Hemlock Spruce. This did not receive a binomial name until Miller named it *Abies americana.* But what was the incident that induced Linnaeus between 1753 and 1763 to establish a new species in this group of plants? Was it from anything Plukenet or Gronovius had written during that decade? Most cerainly not, for one had been long dead and the other had published nothing *new* upon the subject. It is not probable that a reperusal of the old writings had anything to do with the matter as these had already been thoroughly studied for the first edition; also the fact that the synonyms were separated and placed under two species, to neither of which they belonged, is very conclusive evidence that Linnaeus neither knew the Hemlock Spruce nor had any real conception of its status as a species and therefore could not have considered it a type. What then was the controlling factor in the establishment of *Pinus canadensis?* During the decade above referred to Miller published and described under the old style of nomenclature four species of this group and later

illustrated at least one of them, the White Spruce. These publications of Miller brought the species prominently before Linnaeus, who readily recognized the claims of the White Spruce to specific rank and, *on the strength of Miller's publications,* accorded it such as *Pinus canadensis* in the second edition of the Species Plantarum. Rehder claims that the specific name in *Pinus Balsamea* is indicative of what Linnaeus meant, and furthermore that it shows Linnaeus did not get all his information regarding the Balsam Fir from the Hemlock synonyms cited under it. Does not the same reasoning apply when considering *P. canadensis?* Or will Mr. Rehder deny that it does and insist that Linnaeus obtained the specific name *"canadensis" from the writings of Gronovius on Virginia and the Hemlock Spruce?* The entire internal evidence shows conclusively that Linnaeus had the White Newfoundland Spruce in mind when he published *Pinus canadensis* notwithstanding he drew up his diagnosis from Gronovius, which, under the circumstances, was unfortunate. The proper specific name, therefore, for the Hemlock Spruce is the one first applied to it, that of *americana,* and the correct binomial, *Tsuga americana* (Miller) Farwell.

Relative to the Total Nitrogen and α-Amino Nitrogen Content of Pepsins of Different Strengths.

PRELIMINARY COMMUNICATION.

By T. B. Aldrich.

(From the Research Laboratory of Parke, Davis & Co., Detroit.)

About a year ago, I secured a number of pepsins[1] of various strengths from our Digestive Ferment Department, for the purpose of determining what, if any, relation exists between the total nitrogen, the α-amino nitrogen, and the strength of the pepsins, for it was thought that this investigation might throw some light on the nature of pepsin in particular and of enzymes in general.

According to the pharmacopœial tests the strength of the pepsins employed ran all the way from 1:6,000 to 1:15,000 in proteolytic activity; that is, they showed a wide variation in activity and should show some differences along the lines indicated.

The total nitrogen was determined by the official Gunning method.[2] Two blanks were made first with saccharose, using the same reagents and in the same quantities used with the pepsin. Distillation and digestion were carried on for the same length of time in both cases.

The α-amino nitrogen was determined according to the method of Van Slyke,[3] using the larger apparatus. A 4 per cent solution of the pepsin was carefully prepared and 5 cc. of the solution (200 mg. of pepsin) were taken in most instances for each determination. Two determinations were always carried out, sometimes three or four.

Table I gives the results of the total nitrogen determinations; Table II those of the α-amino nitrogen; while Table III gives the average percentages of total nitrogen and α-amino nitrogen in the seven samples employed.

From the table and curve, it is seen that there is a gradual decrease in the percentage of α-amino nitrogen in the samples in the order of their strength. It would seem as though the method used in the purification of the pepsins gradually eliminates the simpler α-amino nitrogen compounds and consequently causes

[1] The pepsins were furnished me by Mr. Harvey Merker, head of the Digestive Ferment Department, and I wish to thank him heartily for the same.

[2] *U. S. Dept. of Agriculture, Bull. 108*, 1912, 7.

[3] Van Slyke, D. D., *Jour. Biol. Chem.*, 1912, xii, 275.

an accumulation of more complex bodies in the stronger pepsins. Taking it for granted that with the still higher pepsins the recognizable α-amino nitrogen content will be further decreased, we would finally by sufficient purification obtain a pepsin having very little detectable α-amino nitrogen or an amount approximating that in the native protein, from which we could infer that the pepsins are of a more complex structure than the simpler α-amino nitrogen compounds—that is, they approach the native proteins in complexity, where, according to Fischer's peptide theory of protein structure, they react with only a trace of their nitrogen, nearly all of the latter being bound in the peptide linkings of the protein molecule. In general the smaller the molecules, the greater the proportion of free amino nitrogen, as has been indicated by the results with the peptides.

The higher pepsins having a strength of 1:8,500 to 1:15,000 contain from 3.08 to 2.06 per cent of α-amino nitrogen, equal to 13 to 20 per cent of the total nitrogen, which compares with the

TABLE I.

Total Nitrogen in the Pepsins.

Pepsin used.	Amount of pepsin.	Acid used. $\frac{N}{10}$ H_2SO_4	Nitrogen obtained.	Nitrogen.
	gm.	*cc.*	*gm.*	*per cent*
No. 74 1:6,000	1.041	107.8	0.151	14.55
	1.095	113.2	0.159	14.57
A.P.B. 1:7,000	1.065	112.0	0.157	14.72
	1.035	108.5	0.152	14.68
	1.124	117.4	0.165	14.64
	1.530	121.0	0.170	14.70
No. 79 1:8,000	1.087	111.6	0.156	14.39
	1.064	108.7	0.152	14.30
No. 00 1:8,500	0.997	100.9	0.141	14.20
	1.026	102.4	0.143	13.98
	1.010	101.5	0.142	14.08
	1.082	109.2	0.153	14.10
No. 1 1:10,000	1.042	105.2	0.147	14.14
	0.995	100.5	0.141	14.15
No. 76 1:11,500	1.014	109.0	0.153	15.06
	0.975	103.4	0.145	14.85
No. 78 1:15,000	1.008	107.7	0.151	14.98
	1.006	106.9	0.151	14.90

TABLE II.

α-Amino Nitrogen in the Pepsins.

Pepsin used.	Amount taken.	Nitrogen.	Temperature.	Barometer.	Nitrogen found.		Average.
	mg.	*cc.*	*°C.*	*mm.*	*per cent*	*mg.*	*per cent*
No. 74 1:6,000	200	13.3	25	748	3.63	7.26	3.65
	200	12.4	25	748	3.39	6.77	
	200	14.2	26	748	3.86	7.71	
	160	11.0	26	748	3.73	5.97	
A. P. B. 1:7,000	200	13.5	30.5	744	3.55	7.11	3.55
	200	13.5	30.5	744	3.55	7.11	
No. 79 1:8,000	200	12.5	25	744	3.39	6.79	3.40
	200	12.6	27	744	3.33	6.77	
	200	12.9	27	744	3.46	6.93	
	160	10.3	28	744	3.45	5.53	
No. 00 1:8,500	200	11.8	28	744	3.14	6.28	3.08
	200	11.6	28	744	3.09	6.18	
	200	11.3	28	744	3.01	6.01	
No. 1 1:10,000	200	10.8	27	747	2.9	5.82	2.98
	200	12.1	28	747	3.2	6.48	
	160	8.6	29	746	2.86	4.58	
No. 76 1:11,500	200	8.5	27	748	2.3	4.59	2.35
	200	8.6	27.5	748	2.4	4.63	
No. 78 1:15,000	200	7.7	26	742	2.06	4.13	2.06
	200	7.9	26	742	2.12	4.24	
	200	7.5	25	742	2.00	4.01	

TABLE III.

No.	Strength of pepsin.	α-Amino nitrogen.	Total nitrogen.
		per cent	*per cent*
74	1:6,000	3.65	14.56
A. P. B.	1:7,000	3.55	14.69
79	1:8,000	3.40	14.35
00	1:8,500	3.08	14.09
1	1:10,000	2.98	14.15
76	1:11,500	2.35	14.96
78	1:15,000	2.06	14.94

α-amino nitrogen obtained by Van Slyke[4] for deutero-albumose. The pepsins may therefore have been either mixtures of native

[4]Van Slyke, *Jour. Biol. Chem.*, 1911, ix, 194.

proteins and their hydrolytic products, or may have consisted entirely of such products of partial hydrolysis as the lower albumoses.

While the percentage of -amino nitrogen shows a constant though slight decrease with increased activity the percentage of total nitrogen in the samples shows very little variation, 14.14 to 14.94 per cent.

It is also interesting to note the following relative to the nitrogen content of *so-called pure* pepsins obtained from different sources and by different methods and authors:

	per cent
Schoumow-Simanowsky[5]	14.55–15.00
Pekelharing[6]	14.13–14.75
Nencki and Sieber[7]	14.33
Bidder and Schmidt[8]	17.80
Chapoteaut[9]	15.4

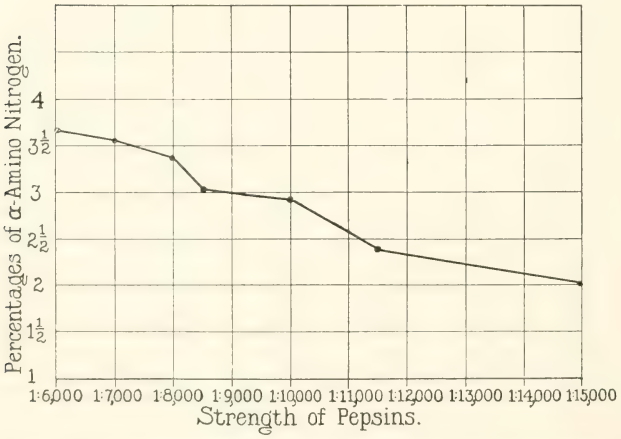


FIG. 1. The curve obtained, with the strength of the pepsins marked along the abscissa at proportional intervals, and the percentages of α-amino nitrogen marked along the ordinate.

[5]Schoumow-Simanowsky, L. O., *Arch. f. exper. Path. u. Pharmakol.*, 1891, xxxiii, 336.

[6]Pekelharing, C. A., *Ztschr. f. physiol. Chem.*, 1902, xxxv, 8.

[7]Nencki, M., and Sieber, N., *ibid.*, 1901, xxxii, 291.

[8]Bidder and Schmidt, Verdauungssäfte, Leipsic, 1852, quoted in Oppenheimer, C., Die Fermente, Leipsic, 1900, 97.

[9]Chapoteaut, P., *Compt. rend. Acad. d. sc.*, 1882, xciv, 1722.

AN EFFECTIVE APPARATUS FOR EVAPORATING AQUEOUS EXTRACTS BY MEANS OF A CURRENT OF AIR.

PLATE 1.

BY T. B. ALDRICH.

(From the Research Laboratory of Parke, Davis & Co., Detroit.)

In certain work in biological chemistry, where gland or plant tissues are to be thoroughly exhausted with water or other solvent, the writer has found it necessary to deal with comparatively large volumes of liquid, the concentration or evaporation of which for further study in the laboratory has presented some difficulties at times, owing to the sensitiveness of the active substance contained in the extract toward heat.

Vacuum concentration has its advantages where contact of the extract with air is known to be harmful, or where the body sought is volatile, and is the only method to be employed under these conditions; however, where the body to be isolated or the solution to be concentrated is not exceptionally sensitive to oxidation but is sensitive to heat, the evaporation by means of a warm blast of air that may be regulated to any temperature, possesses, according to my observation, a number of advantages over the vacuum distillation method.

For example, the method is more rapid, especially at low temperatures; during the evaporation no care is necessary as in the case of vacuum distillation; the cost of evaporation is less; and overheating at any point is avoided.

Unpleasant smelling solutions may be evaporated, since the vapor is carried outside by means of a good drawing flue. The danger of contamination is slight, and may be lessened by passing the air through a suitable thickness of cotton. To avoid any danger, however, the resulting solution may be passed through a Berkefeld filter under proper precautions in case the residual solution is to be used medicinally. In certain cases it has been customary during evaporation to add some harmless volatile antiseptic, such as chloretone, which helps to keep the solution sterile during the evaporation.

The apparatus has been employed for over a year and found very efficient in evaporating aqueous extracts of various glands.

By consulting the accompanying cut and drawing to scale, the construction of the apparatus will become apparent. It has in its favor especially economy of space and efficient utilization of the heated air.

The essential parts of the apparatus consist of a motor and fan, gas burner, and two galvanized iron pipes bent in the form of a U, one enclosing the other. The smaller is attached to the fan at one end while the other end terminates in the hood and is for conveying the heated air obtained from the outside room. This construction avoids mixing the air with the products of combustion, which might injure the products contained in the liquid to be evaporated. The inner pipe just below where it leaves the larger pipe divides into two pipes of equal diameter, containing gates. By this arrangement one or two blasts of air may be employed, or one or both may be cut down as desired. The two terminal pipes have oblong openings 8″ x 1″ respectively and both orifices may be raised or lowered to conform to the height of the dish containing the liquid to be evaporated. All the small pipe inside the hood may be removed in its entirety at any time the space in the hood is required for other purposes. The ordinary laboratory hood lends itself admirably as an exit for the hot air, since it is fairly tight and may be closed if desired, thus forcing the heated air and moisture through the two flues (one is sufficient) to the outside air. The hood pictured has a steam bath flush with the top of the table, which may be used, if desired, for heating the solution from below.

The outer pipe is covered with heavy asbestos and is soldered at one end permanently to the top of the hood; the other open end is just above the circular burner shown in the cut.

When the burner is lit, the inner pipe is heated not only directly by the flame but also by the hot air and gaseous products of combustion which circulate freely through the outer pipe, escaping in part into the hood and in part at the top of the outer pipe through an opening.

The air blast is produced by a No. 1 Sirocco fan (shunt wound motor) made by the American Blower Company. The motor is rated at 1/12 h.p. (120 watts) and produces 1,725 revolutions per

minute at a tension of 120 volts (1 ampere). The volume of air passing through the rectangular orifices per minute is 174 cubic feet when both gates are wide open. (Area of each opening 0.055 square feet; velocity of air current 1,580 feet per minute.)

The following table gives some of the actual results obtained by the use of this apparatus:

	Volume evaporated.	Time of evaporation.	No. of dishes.	Temperature of liquid.	Volume per hr. 2 dishes.
		hrs.		C	*cc.*
1	880	3	2	28–30	293
2	560	3	1	29–30	374
3	200	1	1	29–31	400
4	200	1	1	31	400
5	550	2	1	29–30	550
6	670	2	2	26–29	335
7	380	1½	2	28–30	253
8	420	1½	2	28–30	280

The dishes referred to are of glass and porcelain, have a flat bottom and the dimensions 12″ x 7½″ x 2½″. The surface area of each dish is therefore only 90 square inches. From the tabulated results given above it is seen that even with about the same liquid temperature, the amount evaporated under otherwise similar conditions varies from 253 to 550 cc., or approximately as 1:2. The variation can be accounted for only by the temperature and the varying amount of water vapor of the air. Taking the smallest and largest volumes evaporated in one hour, *viz.*, 253 cc. and 550 cc., we see that it will take from 2 to 4 hours to evaporate 1 liter of liquid. The eight evaporations give an average of 360 cc. per hour, equivalent to 1 liter in three hours. If more rapid evaporation is desired, when there is no danger of injury to the extract, a higher temperature may be obtained by heating the dishes from below, or the water surface may be increased.

An apparatus of somewhat similar construction was employed by Prof. Edwin S. Faust[1] to evaporate extracts susceptible to a temperature over 23°C. This apparatus (a cut of which is given on page 255 in the citation quoted) is arranged horizontally instead of vertically, and its efficiency is less than that of the

[1]Faust, E. S., *Arch. f. exper. Path. u. Pharmakol.*, 1904, li, 255.

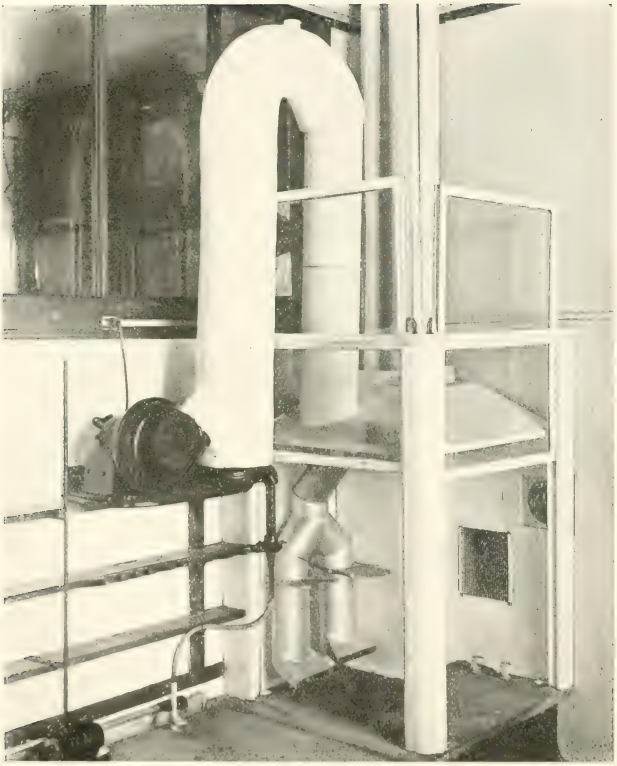


FIG. 1.—Apparatus for evaporating liquids by means of a current of air.
(Aldrich: Evaporation of Aqueous Extracts.)

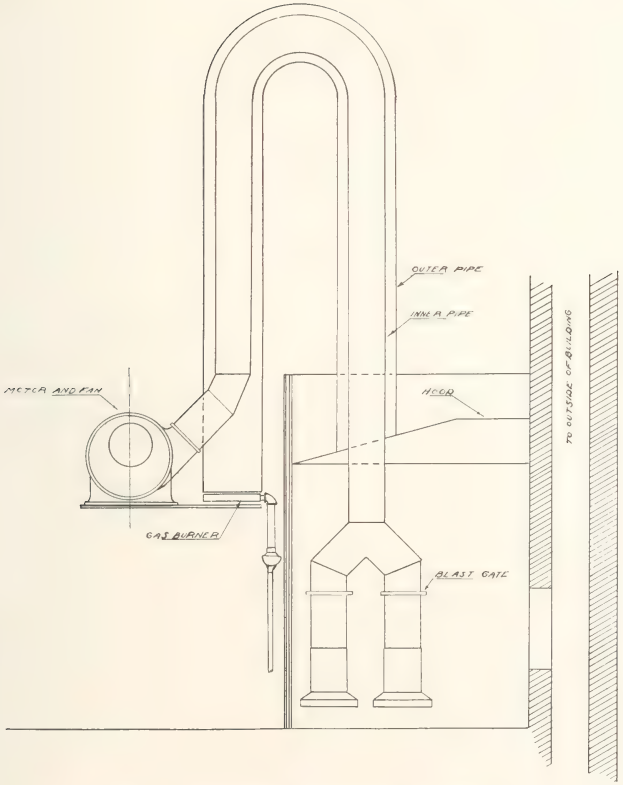


FIG. 2. Vertical section of evaporating apparatus.

apparatus employed in my laboratory. Faust states that 5 to 6 liters of aqueous extract were evaporated in 6 to 8 hours at a temperature of 22-30 . The dishes used in Faust's apparatus had a surface area of about (57″ x 12″) 684 square inches. The two dishes employed in my work have a surface area of 180 square inches or 0.26 of Faust's.

In one instance 360 cc. of aqueous solution were evaporated at 22-26° in one hour; with about four times the area this would mean 1,440 cc. per hour, providing other conditions were the same and the same efficiency prevailed. Faust's efficiency is 5 to 6 liters in 6 to 8 hours or 834-750 cc. per hour. Making liberal allowances, then, for slightly higher temperature, it would seem that the vertical apparatus is more efficient. Faust states that the cost of evaporating 6 liters of liquid is about 12½ cents or about 2 cents per liter. The cost per hour of running the motor in my laboratory is about ¼ cent and the gas consumed per hour is probably not over 1 cent, making a total of 1¼ cents for evaporating over 1 liter of water.

The efficiency of the apparatus might be further increased by placing a horizontal plate of metal as wide as the dish over the liquid to be evaporated, extending from above the rectangular opening to the further end of the dish. This arrangement should ensure closer contact of the air and water and more rapid evaporation.

My thanks are due to Mr. H. E. Whitaker of our Mechanical Department and also to Mr. C. P. Beckwith, my associate, for a number of valuable suggestions relative to the construction of the apparatus.

THE ACTION OF A COAL TAR DISINFECTANT ON HOG CHOLERA VIRUS.

WALTER E. KING AND R. H. DRAKE.

(Research Laboratory, Parke, Davis & Co., Detroit, Mich.)

A few months ago a series of experiments were instituted for the purpose of determining the germicidal activity of Kreso on the virus of hog cholera. In collecting data of this nature, several important conditions must be fulfilled, particularly those involving proper control on the experiments. The virus used in the tests must be sufficiently virulent to cause the death of pigs within approximately fifteen days from the date of inoculation, and typical symptoms and lesions of hog cholera must be present in control animals. Another important factor is the elimination of naturally immune hogs from the series of experiments.

No. Hog	Character of Test	Material Inoculated	Incubation Period	Type of Disease	Date of Death. Duration of Disease from time of exposure.	Character of Lesions
76	Control	2 Cc. Virus (73) 3-5-15	6 Days	Chronic	Recovered in 5 wks.	
141	Control	2 Cc. Virus (161) 8-28-15	3 Days	Acute	9-16-15 19 days	Typical
154	Control	5 Cc. Virus (161) 8-28-15	3 Days	Acute	9-11-15 14 days	Typical
163	1% Kreso Solution	2 Cc. Virus (155) Exposed 5 min. 1% Kreso 8-26-15	6 Days	Sub-acute	9-17-15 22 days	Typical
75	1% Kreso Solution	2 Cc. Virus (73) Exposed 5 min. 1% Kreso 3-5-15	10 Days	Acute	3-23-15 17 days	Typical
164	1% Kreso Solution	2 Cc. Virus (155) Exposed 5 min. 1% Kreso 8-26-15	5 Days	Sub-acute	9-17-15 22 days	Typical
165	2% Kreso Solution	2 Cc. Virus (161)* Exposed 5 min. 2% Kreso 9-1-15	No Symptoms—Released after 20 days			
166	2% Kreso Solution	2 Cc. Virus (161)* Exposed 5 min. 2% Kreso 9-1-15	No Symptoms—Released after 20 days			

The details of this series of experiments consisted in the careful selection of highly virulent virus (serum from hogs infected

*See data above under Hogs No. 141 and 154 which were inoculated with same material as No. 165 and No. 166, except virus was not exposed to action of 2% Kreso Solution. Hogs No. 141 and 154 served as controls on No. 165 and 166.

with hog cholera of acute type) and the addition of a coal tar disinfectant, Kreso, in various dilutions to this virus. The Kreso solution was allowed to remain in contact (in vitro) with the virus for exactly 5 minutes, after which the mixture was injected intramuscularly into healthy pigs. Control pigs received the same dosage of the virus and were cared for under exactly the same conditions as the test animals. The accompanying table compiled from our laboratory data illustrates the nature of these experiments.

The results of these experiments show that highly virulent hog cholera virus (in the form of serum from cholera infected hogs), exposed for five minutes to the action of a two per cent solution of Kreso, is rendered inert.

REPRINTS OF PUBLICATIONS FROM THE RESEARCH LABORATORY, PARKE, DAVIS & CO., DETROIT, MICH.

The present system of collecting reprints of articles published from the Research Laboratory was begun in 1912. Reprints of the following articles published subsequent to that time are available and will be sent upon request. The publications marked (*) are no longer available.

1. On the Administration of Diphtheria Toxin in a Collodion Sac. By E. C. L. Miller. (*Journal of Infectious Diseases,* Vol. 8, January, 1911, pp. 50-65.)

2. A Further Contribution to Our Knowledge of Insecticides—Fumigants. By Chas. T. McClintock, H. C. Hamilton and F. B. Lowe. (*Journal of the American Public Health Association,* Vol. 1, April, 1911, pp. 227-238.)

3. Duboisia Hopwoodii—A Histological Study. By Oliver A. Farwell. (Reprinted from *Merck's Report,* Vol. 20, May 1, 1911.)

*4. Etiology of Canine Distemper. By Newell S. Ferry. (*Journal of Infectious Diseases,* Vol. 8, June, 1911, pp. 399-420.)

*5. The Resistance of Smallpox Vaccine to the Coal-tar Disinfectants. By Chas. T. McClintock and Newell S. Ferry. (*Journal of the American Public Health Association,* Vol. 1, June, 1911, pp. 418-419.)

6. Production of Immunity with Over-Neutralized Diphtheria Toxin. By Chas. T. McClintock and Newell S. Ferry. (*Abdruck Aus Dem Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten,* Abt. 1, Originale, Bd. 59, July 15, 1911, pp. 456-464.)

7. Soaps from Different Glycerides—Their Germicidal and Insecticidal Values Alone and Associated with Active Agents. By H. C. Hamilton. (*Journal of Industrial and Engineering Chemistry,* Vol. 3, August, 1911, pp. 582-584.)

*8. The Sleepy Grass of New Mexico: A Histological Study. By Oliver A. Farwell. (*Merck's Report,* Vol. 20, October, 1911, pp. 271-273.)

*9. Some Observations on the Physiological Action of Sleepy Grass. By A. W. Lescohier. (*Merck's Report,* Vol. 20, October, 1911, pp. 271-275.)

*10. An Investigation of the Depressor Action of Pituitary Extracts. By Carey P. McCord. (*Archives of Internal Medicine,* Vol. 8, November, 1911, pp. 609-620.)

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14. The Relations of Pyogenic Microorganisms to the Etiology and Treatment of Skin Diseases. By Henry Rockwell Varney. (*Ohio State Medical Journal,* December, 1911.)

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16. Serum Treatment of Hemorrhage and Blood Dyscrasias. By A. W. Lescohier. (*New York Medical Journal,* Vol. 95, February 3, 1912, pp. 223-229.)

*17. Further Studies on the Bacillus Bronchicanis, the Cause of Canine Distemper. By Newell S. Ferry. (*American Veterinary Review,* Vol. 41, April, 1912, pp. 77-79.)

18. The Pharmacopœial Requirements for Cannabis Sativa. By H. C. Hamilton. (*Journal of the American Pharmaceutical Association,* Vol. 1, March, 1912, pp. 200-203.)

19. The Heart Tonic Unit. By H. C. Hamilton. (*American Journal of Pharmacy,* Vol. 84, March, 1912, pp. 97-103.)

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28. Pituitary Extracts in Obstetrics and Gynecology. By A. W. Lescohier and O. E. Closson. (*Journal of the Michigan State Medical Society,* Vol. 11, October, 1912, pp. 650-657.)

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62. Some Experiences with Bacterial Vaccines in Scarlatina. By Guy L. Kiefer, M.D., D.P.H., and N. S. Ferry, M.D. (*Medical Record,* Vol. 85, May 23, 1914, p. 936.)

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65. The Bacteriological Standardization of Disinfectants. By H. C. Hamilton and Tatsuzo Ohno. (*American Journal of Public Health,* Vol. 4, No. 6, p. 163.)

66. The Pineal Gland in Relation to Somatic, Sexual and Mental Development. By Carey P. McCord, M.D. (*Journal of the American Medical Association,* Vol. 63, July 18, 1914, pp. 232-235.)

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83. The Correct Name for the Hemlock Spruce. By Oliver A. Farwell. (*Bulletin of the Torrey Botanical Club,* 41, Jan. 8, 1915, pp. 621-629.)

84. The Proper Time to Collect Sanguinaria. By O. A. Farwell. (*American Journal of Pharmacy,* Vol. 87, March, 1915, pp. 97-98.)

85. Notes on the Michigan Species of Polygonatum. By O. A. Farwell. (*Bulletin of the Torrey Botanical Club 42,* May, 1915, pp. 247-258.)

86. Belladonna and Hyoscyamus. By O. A. Farwell. (*American Journal of Pharmacy,* March, 1915, pp. 99-101.)

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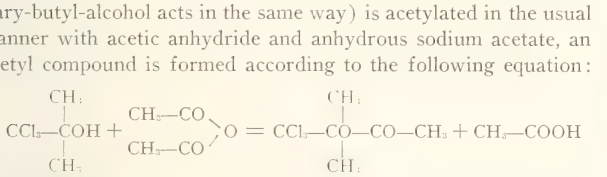
MONO-ACETYL-TRI-CHLOROTERTIARY-BUTYL-ALCOHOL. (ACETYL CHLORETONE.)

By T. B. Aldrich.

(From the Research Laboratory of Parke, Davis & Co.)

When trichlorotertiary-butyl-alcohol (presumably tri-bromotertiary-butyl-alcohol acts in the same way) is acetylated in the usual manner with acetic anhydride and anhydrous sodium acetate, an acetyl compound is formed according to the following equation:



Preparation.—One (1) part of chloretone was boiled with two (2) parts of acetic anhydride and one (1) part of anhydrous sodium acetate for two hours, using a reflux condenser. The solution, after cooling and diluting with water, was neutralized with sodium carbonate and subjected to steam distillation, the acetyl derivative passing over with the steam in the form of an oil that was practically colorless. The oil was collected with ether, the ethereal solution washed with water, then dried with calcium chloride, and finally filtered through a dry filter into a tared vessel. After evaporating the ether the residual oil gave, in one instance, a yield of about 80%. Slight decomposition took place when the oil was distilled at ordinary temperature; however, the greater part went over between 180-190° as a nearly colorless oil. When distilled in partial vacuum at 246 mm. the substance boiled fairly constantly without any apparent decomposition at 145-146° and gave a yield of 85% of the amount started with. Chloretone under the same conditions (pressure, etc.) boils at 134-136°.

Combustion and chlorine determinations were made with a product, boiling at 151-153° under 250 mm. pressure. The bulb for holding the liquid for analysis was weighed empty, then warmed, and the neck of the bulb which had been drawn to a fine tube immersed in the acetyl chloretone. When, on cooling, sufficient oil had entered the bulb, it was reweighed.

The analytical results for carbon were somewhat lower and for

chlorine somewhat higher than the calculated values, indicating the presence of some unchanged chloretone. This was verified by the results of the purification treatment.

In order to remove traces of chloretone, the acetyl compound already analyzed was heated on the steam bath for 20 min. with 100 cc. of a 10% NaOH solution in order to decompose the chloretone present. The acetyl derivative, which was unaffected by this treatment, was then collected with ether, washed, dried, and distilled in the usual manner under reduced pressure. The substance distilled at 151-152° under a pressure of 237 mm. The following chlorine determination (Carius) is sufficient to show that this compound is practically pure:

0.3831 g. gave 0.7535 g. AgCl or 0.1864 g. Cl.
Calc. for $C_8H_9O_2Cl_3$: 48.63%. Found: 48.65%.

Three cc. of the acetyl compound were placed in a pressure tube with 10 cc. of H_2O and heated for 3 hours at 160°. On opening the tube there was no apparent change. On heating the resealed tube for 3 hours at 250° complete decomposition of the substance took place, and on opening the tube there was considerable pressure. The substance was in part carbonized, but there was no evidence of chloretone, the reaction of the liquid was acid and $AgNO_3$ gave a precipitate soluble in NH_4OH.

Two cc. of the acetyl compound were placed in a sealed tube with 25 cc. H_2O and heated to 160° for 8 hours. On opening the tube, there was considerable pressure, and a reddish-brown oil was noticed (½ cc.) at the bottom of the tube, the supernatant liquid being slightly yellow. Its reaction was strongly acid and $AgNO_3$ gave a voluminous precipitate soluble in NH_4OH.

When boiled with water for a long time (108 hours), using a reflux condenser, some crystals resembling chloretone were observed in the condenser and neck of the flask (that is, on standing over night). These were collected on a filter, dissolved in dilute alcohol and recrystallized. White needles; taste and smell like chloretone. M. p. 78°.

When acetyl chloretone is boiled with water to which H_2SO_4 has been added, the saponification takes place much more rapidly. Boiling 7 hours is sufficient to obtain considerable chloretone in the condenser tube.

Although saponification takes place slowly by boiling with

water, or water and dilute acids, it is extremely interesting to note that saponification takes place very rapidly when the ester is boiled with an excess (three or four times its volume) of *concentrated* nitric acid. Indeed, after boiling only a few minutes a large amount of chloretone may be thrown out of the acid solution in a crystalline form by the addition of water.

The solubilities of the acetyl ester are practically the same as those of chloretone. It dissolves very readily in alcohol, acetone, ether, chloroform, benzene, etc., and is *practically insoluble* in water, even less soluble than chloretone. (Upon placing 0.5 g. in 100 cc. measuring flasks and adding water to mark, very little, if any, passed into solution after shaking occasionally for several days.)

It is volatile, though less so than chloretone.

(1) 1 cc. was placed on watch glass and allowed to stand at room temperature; at the end of 14 hours ½ had evaporated.

(2) 1 cc. was placed in incubator at 37°; at the end of 14 hours it had evaporated completely.

Acetyl chloretone has anesthetic properties similar to chloretone and brometone; but, since it is so slightly soluble in water, its effect does not appear for several hours, and therefore it cannot be used to advantage as a substitute for chloretone for inducing general anesthesia in animal experiments. On account of its more agreeable odor, it might be used in some instances to advantage in place of chloretone. The toxicity of the acetyl ester, when introduced subcutaneously into guinea pigs, is slightly less than that of chloretone; its bactericidal efficiency was not tested.

It is generally accepted that the esters of the tertiary alcohols, on heating alone above their boiling point in a sealed tube, are decomposed into acids and unsaturated hydrocarbons,[1] and we might expect a similar behavior in the case of acetyl-trichloro-tertiary-butyl-alcohol when heated similarly. The decomposition products of acetyl chloretone when heated *alone* were not determined, but with water or acids it gave rise, in part as far as could be observed, to chloretone without the above decomposition.

[1] Lassar-Cohn, "Arbeitsmethoden." 3d ed., p. 1152.

THE OCCURRENCE OF PITUITRIN AND EPINEPHRIN IN FETAL PITUITARY AND SUPRARENAL GLANDS.

By Carey Pratt McCord.

(From the Research Laboratory of Parke, Davis & Co., Detroit.)

(Received for Publication, October 4, 1915.)

For the growth of the fetus *in utero* it is undetermined whether the greater influence is exerted by the maternal internal secretory system or by the newly formed glands of the fetus itself. The added strain incident to pregnancy is evidenced in the mother's glandular system by such functional hyperplasias as the frequently observed hyperthyroidism or the altered facies indicative of a mild, transient acromegaly from hyperpituitarism. At what period of development the embryo comes under the influence of the secretions of its own glands is not known. An investigation to establish the earliest developmental period in which it is possible to detect the presence of the glandular secretions in the glands themselves would be of value to the full solution of this problem. The work which led to this report was the examination of the pituitary and suprarenal glands of bovine fetuses, from full term back as early as the macroscopic recognition of the glands was possible, in an effort to establish the stage at which these glands commence the elaboration of their active principles.

Forty-two embryos in various developmental phases were procured in fresh condition from the abattoirs. In those that were at or near full term, no difficulty was encountered in the separation of the anterior and posterior lobes of the pituitaries. In younger embryos separation was not possible and the entire gland was tested. In the youngest fetuses it was necessary to freeze the bodies to facilitate the removal of the glands. To provide sufficient material to bring about the characteristic physiologic reactions, several of the youngest embryos of approximately the same ages were grouped and tested as one. In every instance, the material was extracted with distilled water and the extract freed of protein contamination.

The presence of the active principle of the pituitary was measured in terms of oxytocic activity by means of the method of

Dale and Laidlaw[1] with histamine (β-imidazolyl ethylamine) as a standard (Roth[2]). This oxytocic test under optimum working conditions has proven qualitatively active with special pituitary preparations in dilutions 1 to 1,000,000,000. Since these especially prepared pituitary preparations are known to be five times as active as histamine, the statement above is grossly in accord with that of Roth that the test is sensitive to 1 part of histamine in 250,000,000. As a method of quantitative assaying, this oxytocic test requires the most exact technique. With proper consideration for the many apparently trivial causes of error,exquisitely accurate results may at times be obtained. As a routine procedure for the accurate standardization of a large number of preparations, the method is not attended with such ease of manipulation as is suggested in some of the published articles descriptive of this test.

The presence or absence of epinephrin in the adrenal glands was detected through observations of the influence of the several extracts in relaxing the contracted uterine muscles of rodents. The tests were made upon such guinea pig uterine muscles as were refractory in that there occurred no ready spontaneous relaxation after being stimulated to contraction by histamine. Earlier Fenger[3] examined the suprarenals of fetuses for the presence of the crystalline epinephrin. He was able to recover epinephrin in all fetuses examined, but his studies did not include the early weeks of development. This writer also points out the occurrence of iodine in fetal thyroids.

The tests for pituitrin were begun with embryos at or near full term. Such tests and others back as early as nine weeks were quantitative tests. Pituitrin was present in all extracts, and the quantity for a unit of weight was larger than for the adult. The quantity present in the several stages examined was in proportion to the stage of development. At a period represented by the seventh and eighth weeks, the contents of the cranium were grossly only a viscid mass in which the pituitary could no longer be recognized although the sella turcica was plainly visible. Physiologic testing of the pituitary was not feasible for this or any earlier stage. It may be recalled that at this approximate stage the developing anterior lobe encloses and invades the *pars nervosa*

[1] Dale, H. H., and Laidlaw, P. P., *Jour. Pharm. and Exper. Therap.*, 1912-13, iv, 75.
[2] Roth, G. B., *Bull. Hyg. Lab., U. S. P.H. and M.H.S.*, No. 100, 1914, 5.
[3] Fenger, F., *Jour. Biol. Chem.*, 1914, xix, 35.

with a layer of cells that later becomes the *pars intermedia*, which probably is the actual secreting portion of the posterior lobe. Thus the testing for pituitrin is positive at a time which approximated the earliest period when on theoretical grounds secretion is at all probable.

The parallel testing of the adrenal extracts for physiologic evidence of the presence of epinephrin indicates that epinephrin was present at all stages examined. Even when the pituitaries were no longer obtainable in the very young embryos, the adrenals were distinct entities and readily obtainable. At the end of the sixth week, the epinephrin tests were distinctly positive.

Further details as to weights, ages, etc., are grouped in the table that follows.

SUMMARY.

Physiologic reactions characteristic of extracts of pituitary and suprarenal glands have been obtained from bovine fetal glands during all developmental stages in which the macroscopic recognition of the glands is possible. For the pituitary gland, this period is from the eighth week to full term; for the suprarenals the period is from the sixth week to full term. The presence of the active principles of these glands at so early a developmental period suggests that the fetus *in utero* may be under the influence of its own internal secreting glands as well as the maternal glands.

The Occurrence of Pituitrin and Epinephrin in Fetal Glands.

Group.	No.	Length of fetus.	Approximate age.	Weight of pituitary.		Weight of suprarenal (both glands).	Oxytocic testing.		Remarks.
				Whole.	Posterior lobe.		Pituitary.	Suprarenal.	
		mm.	*days*	*gm.*	*gm.*	*gm.*			
I	1	113	55			0.0345	Pituitary not recognizable	Active	The 5 embryos were grouped and tested as one.
	2	127	59						
	3	130	60						
	4	140	63			0.0336			
	5	152	65						
II	6	165	67			0.0764	Active	Active	Nos. 6, 9, and 11 were grouped together to be tested. Extract made from the pituitary glands removed from Nos. 7, 8, 10, and 12 was tested quantitatively.
	7	♀ 175	68	0.0032	0.0016	0.099	"	"	
	8	♀ 187	69	0.015	0.0048	0.087	"	"	
	9	201	70	0.0214		0.145	"	"	
	10	♀ 213	72	0.0105	0.0035	0.09	"	"	
	11	218	73	0.023		0.156	"	"	
	12	♀ 220	74	0.0165	0.006	0.109	"	"	
III	13	♀ 223	75	0.0185	0.0066	0.113	"	"	Nos. 14, 15, 16, and 17 were grouped together to be tested. No. 13 was tested quantitatively.
	14	225	75	0.0278		0.0824	"	"	
	15	235	75	0.0238		0.102	"	"	
	16	240	76	0.0325		0.102	"	"	
	17	245	76			0.161	"	"	
IV	18	250	77	0.034		0.160	"	"	Nos. 18, 19, and 20 were grouped together to be tested.
	19	250	77	0.03		0.134	"	"	
	20	265	79			0.15	"	"	
V	21	270	80	0.0922		0.222		"	Nos. 21, 22, and 24 were grouped together and tested. The extract made from the pituitary glands removed from Nos. 23, 25, 26, and 27 was tested quantitatively.
	22	275	81			0.171		"	
	23	♂ 280	82	0.026	0.009	0.180	"	"	
	24	290	83	0.0224		0.122		"	
	25	♂ 298	84	0.032	0.0085	0.139	"	"	
	26	♀ 300	140	0.0415	0.0065	0.209	"	"	
	27	♀ 320	150	0.04	0.0105	0.268	"	"	

THE PRINCIPLES OF VACCINE THERAPY AND WHY IT SHOULD BE USED IN THE TREATMENT OF PYORRHEA.

GEORGE BAILEY HARRIS, D.D.S., SC.M., AND E. M. STANTON.

(From the Research Laboratory, Parke, Davis & Company, Detroit, Mich.)

Abstracted from *The Dental Summary*, October, 1915.

Vaccine therapy in pyorrhea is to be considered an adjunct not a substitute for surgical treatment. The application of vaccines conceives that the disease is of an infectious nature and is based upon the established principles of immunity. Failure on the part of the phagocytic leucocytes to control the infectious process may be due to walling off of the infection, thus mechanically protecting the organisms from phagocytosis; or to a deficiency of the specific antibodies upon which immunizing protection depends. The walling off of the infection may be overcome by instrumentation; the antibody deficiency by vaccine treatment.

I do not have the time to take up the work with the various organisms found in pyorrhea, but will say that the work done points strongly to the streptococcus. We have been unable to produce pyorrhea in animals with any other organism or combination of organisms. The staphylococcus likely plays an important secondary rôle, as it liberates toxins keeping the upper portions of the infected area inflamed and on the defensive. The pneumococcus plays a very minor rôle, if, indeed, it is involved at all. We do not believe it to be involved, but have not succeeded as yet in positively proving it.

In regard to the relative merits of the stock and autogenous vaccines, I would say that I must give the preference to the autogenous, but I do not use them exclusively due to the time required in making them. In all cases where a stock vaccine fails to give a response after the third or fourth injection an autogenous vaccine should be resorted to.

During the last three years I have been working on stock vaccines in an effort to produce one that would produce equally good results as an autogenous in the majority of cases. As a result of this work a combination has been evolved that has given results equal to those obtained by the use of autogenous vaccines in all cases in which it has been used, so far as I have been able to find out. This vaccine is composed of various strains of the strepto-

coccus, staphylococcus and pneumococcus in the following proportions: Streptococcus 40,000,000, staphylococcus albus 200,000,000 and pneumococcus 40,000,000. It is marketed by Parke, Davis & Co. in the syringe, four bulbs containing one c.c. each, and in bulk form containing five c.c. and 20 c.c. The contents of the bulb may be withdrawn in two ways—by removing the cork or by first dipping the rubber cork in phenol, then alcohol, and forcing the needle through the cork. The handiest way to use the vaccine is the syringe package. The needle comes wrapped in a sterile container and is sterilized.

DOSAGE.

Success or failure in vaccine therapy depends more on the dosage than any other one thing, nor is there any set rule in regard to the dosage that could be followed. In this regard every patient is a law unto himself. The time allowed to lapse between doses is also an important thing to be considered in their use. The first effect of the administration of a dose of vaccine is generally to depress the index, and if the dose be large a marked and long depression of the opsonic index may result.

In utilizing the vaccine previously referred to, it has been customary to give as an initial dose 0.5 c.c. (20 million streptococcus, 100 million staphlococcus albus and 20 million pneumococcus.) Subsequent injections are usually given at intervals of from 3 to 5 days, and unless there are indications to the contrary, it is advisable to increase the dose 0.1 to 0.2 c.c. at each injection, until a maximum dose of 1 c.c. has been reached. In many cases it will be found necessary to give repeated injections of this maximum dose before definite clinical results are obtained. If marked reaction follows any of the injections it is unwise to increase the dose at that time. Under such circumstances the same or a smaller dose should be given until marked reaction is no longer elicited after which the dosage may be slowly increased.

EXPLANATION OF CUTS.

Fig. 1. In this case there was severe pain in the lower teeth. This was due to an active streptococcic infection. After scaling the teeth one-half c.c. of the pyorrhea vaccine was given. This dose was repeated five days later. In all seven injections were given, the last two being one c.c. each. The pus ceased after the third injection. The soreness left three days after the first injec-

tion. An examination a year after showed no signs of return and he has tight teeth today.

Supposing, however, the serum of an uninjected individual suffering from pyorrhea be compared with the control film and we count 200 for the normal and only 100 for the abnormal—

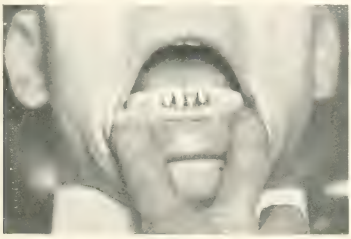


Fig. 7.

100-200 times 1=0.5. The phagocytic power of this individual is .5 or one-half what it should be, and under such conditions recovery from pyorrhea is improbable. Six injections of vaccine changed the index to 1.4, the discharge of pus stopping, all sore-

Fig. 8.

ness being removed. There is a new tissue growth taking place and the teeth are tighter than they have been for some time. He is still under treatment (Fig. 8).

Since this paper was read, this case has completely recovered and has tight teeth today.

In this case (Fig. 9) the first effect of the vaccine was to depress the index from 1.1 to 0.7, the depression lasting for two days. Sometimes before there is a depression there is a rise in

the index. Were another injection given during this false rise a summation of negative phases would be the result. This is something that should be carefully guarded against. This is followed by a rise in the index to 1.5, after which the index falls again, and on the seventh day after inoculation the index is 1.2, returning to normal three weeks later. From this record it will be seen that this individual should receive an injection every four days, increasing the dose 1-10 c.c. at each injection. In this case five injections were required to overcome a streptococcus infection.

The most serious of conditions coming under this classification

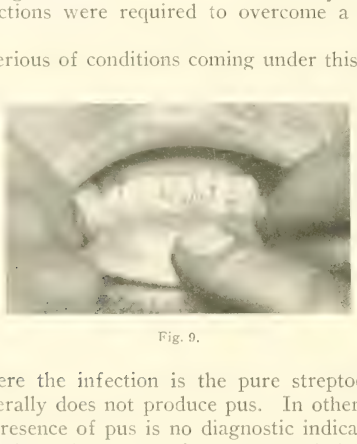


Fig. 9.

are those where the infection is the pure streptococcus. This organism generally does not produce pus. In other words, presence or non-presence of pus is no diagnostic indication that it is or is not pyorrhea; the most serious cases and those capable of

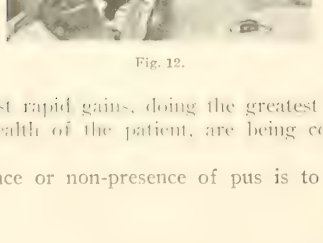


Fig. 12.

making the most rapid gains, doing the greatest damage to the alveolus and health of the patient, are being completely overlooked.

If the presence or non-presence of pus is to be taken as a

diagnostic indication as to whether bacterial vaccines are indicated or not, vaccines are not being used in the cases where they are needed most.

This is not theory, but it is based on definite findings in a large number of just such cases with unusually good results with vaccine therapy. In my experiments, a dog developing pyorrhea either naturally or artificially produced, usually dies within a month. A general infection follows rapidly unless checked by previous treatments of vaccines.

Fig. 12. This dog was infected with 100,000,000 staphylococcus aureus with no result. 20,000,000 pneumococcus was then planted between the alveolus and the root. No result. Staphylococcus albus was tried with no result; finally streptococcus (10,000,000 attenuated) was used, which rapidly produced pyorrhea and as rapidly passing on into a general infection causing a discharge from the nose, resulting in the death of the dog seventeen days after inoculation. Upon examination cultures of the streptococcus were obtained from the liver, kidneys and heart blood.

Fig. 13. Streptococcus was planted in the molar tooth, which was previously devitalized. What happened? A marked inflammatory condition developed all along the gum margins, followed by a slight recession of the gums. This was rapidly followed by a general infection resulting in the death of the dog twenty-two

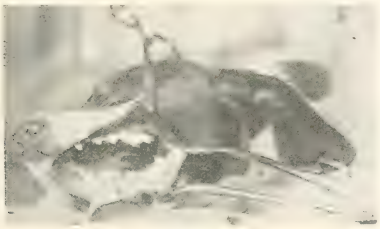


Fig. 13.

days after the streptococcus was planted in the root. The streptococcus was then recovered from the liver, heart blood, kidneys and spleen.

These two cases do not clearly show pyorrhea owing to the very rapid development of a general infection.

Fig. 14. This is generally the rule. However, this shows a case where the dog was able to resist a general infection, resulting in a marked case of pyorrhea.

Fig. 14.

Fig. 15. This gentleman had undergone local treatment for pyorrhea for about one year. At the end of that time he was not able to eat a meal without severe pain. His opsonic index was

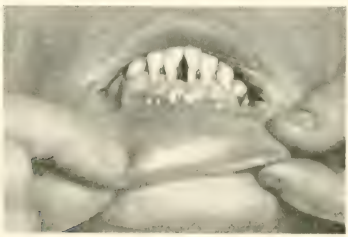


Fig. 15.

low to streptococcus. Pus was present. Cultures showed streptococcus predominating, staphylococcus albus producing the pus; three injections of vaccine given five days apart stopped the pus.

The opsonic index still remained below normal to streptococcus .85, but above normal to staphylococcus 1.1. An increased dose given three times five days apart resulted in a rapid rise in the index to 1.5 for streptococcus and 1.7 to staphylococcus albus. All soreness left the teeth when this point was reached and the gums took on a healthy appearance. Granulations followed this. The teeth are becoming firmer. Vaccines are still being used, small doses given every two weeks to maintain a high index, this preventing a recurrent infection.

Fig. 16. In this case the opsonic findings were .7 to streptococcus, 9 to albus. Injections given in this case were .5 c.c. stock

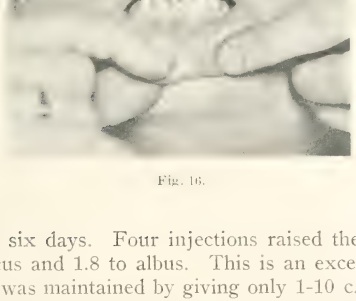


Fig. 16.

vaccine every six days. Four injections raised the index to 1.7 to streptococcus and 1.8 to albus. This is an exceptionally high index, which was maintained by giving only 1-10 c.c. every three weeks. All discomforts disappeared as the index went above normal. The teeth are becoming tighter and a complete recovery is expected.

Fig. 17. Complete recovery followed vaccine treatment in this case. Two injections of pyorrhea vaccine caused a disappearance of all pus. Before injection the index was .5 to streptococcus, normal to albus. After two injections the index was 1.4 to streptococcus, 1.7 to albus. The pulps in the lower molar teeth were killed by the infection. These teeth were not loose enough to destroy pulp. A streptococcus infection was found in the pulp. The whole upper and lower jaw was involved, bicuspids and

molars on the upper left being loose. Also the lower central and lateral incisors.

This gentleman does not have a loose tooth in his head today and is enjoying three good meals a day.

Fig. 17.

Fig. 18. In this case there was a very active streptococcus infection. The patient was not able to bring his teeth together due to the severe pain. Instrumentation was impossible, due to the intense pain. His mouth was completely filled with pus. Two injections of stock vaccine reduced the amount of pus to such an

Fig. 18.

extent that he was able to close his jaws without pain and instrumentation could be resorted to. Four more injections of vaccine caused a secession of pus. The teeth are now tight and normal condition has been brought about.

Fig. 19. Here is a milder form of a streptococcus. The pockets around the centrals were very deep, reaching to the apex of the root in the left central. This tooth was quite loose. Recession of the gums had just started around this tooth. The other central was tight and not affected much. The pyorrhea

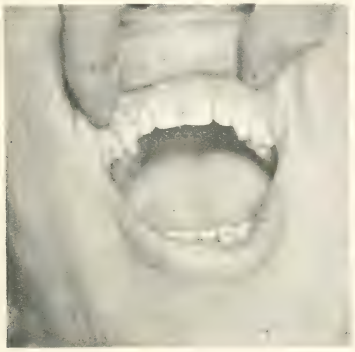


Fig. 19.

seemed to be confined to these two teeth. Five injections of the stock vaccine made it impossible to obtain a culture of streptococcus. This pocket filled in completely in five months' time.

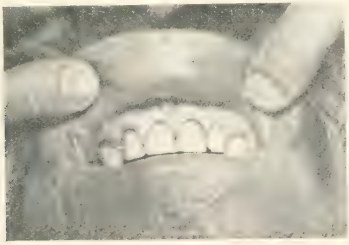


Fig. 20.

Fig. 20. This gentleman suffered with neuralgia for a year, during which time he was treated by his physician. He was referred to me, and a careful examination revealed a streptococcic

infection in the centrals and laterals and cuspids. There was no pus present. He was kept under local treatment for one month, during which time there was no change in his condition. Vaccines were then used, he receiving eight doses of the stock vaccine. After the third dose all pain disappeared. A culture was taken at this time and a very small amount of streptococcus was found in one pocket. An examination eight months after showed complete recovery.

REPRINTS OF PUBLICATIONS FROM THE RESEARCH LABORATORY, PARKE, DAVIS & CO., DETROIT, MICH.

The present system of collecting reprints of articles published from the Research Laboratory was begun in 1912. Reprints of the following articles published subsequent to that time are available and will be sent upon request. The publications marked (*) are no longer available.

1. On the Administration of Diphtheria Toxin in a Collodion Sac. By E. C. L. Miller. (*Journal of Infectious Diseases,* Vol. 8, January, 1911, pp. 50-65.)

2. A Further Contribution to Our Knowledge of Insecticides—Fumigants. By Chas. T. McClintock, H. C. Hamilton and F. B. Lowe. (*Journal of the American Public Health Association,* Vol. 1, April, 1911, pp. 227-238.)

3. Duboisia Hopwoodii—A Histological Study. By Oliver A. Farwell. (Reprinted from *Merck's Report,* Vol. 20, May 1, 1911.)

*4. Etiology of Canine Distemper. By Newell S. Ferry. (*Journal of Infectious Diseases,* Vol. 8, June, 1911, pp. 399-420.)

*5. The Resistance of Smallpox Vaccine to the Coal-tar Disinfectants. By Chas. T. McClintock and Newell S. Ferry. (*Journal of the American Public Health Association,* Vol. 1, June, 1911, pp. 418-419.)

6. Production of Immunity with Over-Neutralized Diphtheria Toxin. By Chas. T. McClintock and Newell S. Ferry. (*Abdruck Aus Dem Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten,* Abt. 1, Originale, Bd. 59, July 15, 1911, pp. 456-464.)

7. Soaps from Different Glycerides—Their Germicidal and Insecticidal Values Alone and Associated with Active Agents. By H. C. Hamilton. (*Journal of Industrial and Engineering Chemistry,* Vol. 3, August, 1911, pp. 582-584.)

*8. The Sleepy Grass of New Mexico: A Histological Study. By Oliver A. Farwell. (*Merck's Report,* Vol. 20, October, 1911, pp. 271-273.)

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